

Guidelines for management of thyroid cancer

British Thyroid Association

Royal College of Physicians

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Notes on the development and use of the guidelines

Development of the Guidelines

The Thyroid Cancer Guidelines were first published in 2002 after extensive review of the literature by representatives of professional and patient-led organisations (Royal Colleges of Physicians, Radiologists, Surgeons, Pathologists, General Practitioners, Nurses, the British Association of Endocrine Surgeons, the British Association of Otolaryngologists and Head and Neck Surgeons (BAOL-HNS), the British Association of Head and Neck Oncologists of Great Britain (BAHNO), the British Nuclear Medicine Society, the Society for Endocrinology and the British Thyroid Foundation) and external refereeing.

The guidelines were updated in 2006 by a subgroup representing the majority of the same professional organisations, in the light of recent advances in diagnosis and management of thyroid cancer. The updated guidelines place emphasis on tailoring the aggressiveness of treatment and monitoring to the individual patient, and the central role of the Multidisciplinary team meetings in making these decisions based on risk assessment. In addition, the updated guidelines incorporate issues that have arisen as a result of the implementation of waiting times of the Cancer Plan and the publication of “Improving Outcomes in Head and Neck cancer” by the National Institute of Clinical Excellence in 2004¹.

The updated guidelines were reviewed by several members of the original guideline group and by other external referees before publication.

The intention is that the guidelines be adopted by the individual Regional Cancer Networks, after discussion by local clinical and managerial staff, and with the addition of appropriate arrangements, for use in the specific centres.

This document should be considered as a guideline only; it is not intended to serve as a standard of medical care. It should not be construed as including all the acceptable methods of care. The management plan for an individual patient must be made by the Multidisciplinary team in the light of the clinical data and the diagnostic and treatment options available.

The focus of the document is the management of thyroid cancer, rather than investigation of thyroid nodules. The guideline focuses mainly on thyroid cancer in adult patients although childhood thyroid cancer is included in the section on medullary thyroid cancer. Guidelines on thyroid cancer in children can be found elsewhere².

It is hoped that the document will provide guidance for primary care physicians, general physicians, endocrinologists, surgeons, oncologists, nuclear medicine physicians, radiologists, medical physicists, biochemists and nurses, as well as those involved in managerial roles.

The guidelines are also intended to provide a basis for local and national audit and each section offers recommendations that are suitable for the audit process.

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These guidelines may be photocopied or down-loaded from the BTA web site:
www.british-thyroid-association.org

Types of evidence and the grading of recommendations

The definition of Types of Evidence and the Grading of Recommendations used in the guidelines follows that of the Agency for Health Care Policy and Research (AHCPR), as set out below:

Type of evidence (based on AHCPR 1992³)

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of recommendations (based on AHCPR 1994⁴)

Grade	Evidence levels	Description
A	Ia, Ib	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B	IIa, IIb, III	Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C	IV	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

Abbreviations

AHCPR:	Agency for Health Care Policy and Research (now Agency of Health Research and Quality)
ARSAC:	Administration of Radioactive Substances Advisory Committee (part of Health Protection Agency).
BATES:	British Association of Thyroid and Endocrine Surgeons
BAOL- HNS:	British Association of Otolaryngologists/Head & Neck Surgeons
CCH:	C-Cell hyperplasia
DTC:	Differentiated Thyroid Cancer*
FACS:	Fluorescent Activated Cell Sorter
FDG:	¹⁸ Fluoro-Deoxy-Glucose
FMTC:	Familial Medullary Thyroid Cancer
FNAC:	Fine Needle Aspiration Cytology
FTC:	Follicular Thyroid Cancer*
GP:	General Practitioner
IJV:	Internal Jugular Vein

IMR:	Intensity Modulated Radiotherapy
IRMA:	Immunoradiometric Assay
MACIS:	<u>M</u> etastases, <u>A</u> ge at presentation, <u>C</u> ompleteness of surgical resection, <u>I</u> nvasion (extrathyroidal), <u>S</u> ize
MALT:	Mucosa Associated Lymphoid Tissue
MDL:	Minimum Level of Detection
MDT:	Multi Disciplinary Team
MEN:	Multiple Endocrine Neoplasia
MRND:	Modified Radical Neck Dissection
MTC:	Medullary Thyroid Carcinoma*
PET:	Positron Emission Tomography
PTC:	Papillary Thyroid Cancer*
PTH:	Parathyroid Hormone
pTNM:	<u>P</u> athologically staged according to <u>T</u> umour size, <u>N</u> ode metastases and distant <u>M</u> etastases
rhTSH:	Recombinant human TSH
RIA:	Radioimmunoassay
SAN:	Spinal Accessory Nerve
SCM:	Sternocleidomastoid muscle
T3:	Triiodothyronine (liothyronine)
T4:	Thyroxine (levothyroxine)
TFT:	Thyroid function tests
Tg:	Thyroglobulin
TgAb:	Anti-thyroglobulin Antibodies
TSG:	Tumour Specific Group
TSH:	Thyroid Stimulating Hormone
WBS:	Whole Body Scan

***Definitions of types of thyroid cancer used in the guidelines:**

Thyroid Cancer: Any primary thyroid malignancy (includes differentiated thyroid cancer, medullary thyroid cancer anaplastic thyroid cancer, thyroid lymphoma and other very rare types).

Differentiated thyroid cancer: Papillary thyroid cancer and follicular thyroid cancer (includes Hürthle cell carcinoma)

Key recommendations and overview of management of thyroid cancer (differentiated and medullary)

These guidelines refer to the investigation and management of differentiated (papillary and follicular) and medullary thyroid cancer.

1 Access to a multidisciplinary thyroid cancer team

- i. The management of differentiated thyroid cancer (a highly curable disease) and of medullary thyroid cancer should be the responsibility of a specialist multidisciplinary team (MDT), membership of which will normally be appointed by the Regional Cancer Network⁵ **(IV, C)**.
- ii. The timeframe for urgent referrals should comply with the Department of Health targets (section 2) **(IV, C)**.
- iii. The MDT will normally comprise surgeon, endocrinologist and oncologist (or nuclear medicine physician) with support from pathologist, medical physicist, biochemist, radiologist, specialist nurse, all with expertise and interest in the management of thyroid cancers **(IV, C)**.
- iv. Patients will normally be seen by one or more members of the MDT; a combined clinic is recommended. All members of the MDT should maintain continuing professional development **(IV, C)**.

2 Patient focus

- i. Patients should be offered full verbal and written information about their condition and their treatment (Appendix 5) **(IV, C)**.
- ii. Patients should have continuing access to a member of the MDT for guidance and support **(IV, C)**.

3 Surgery (section 5)

The surgeon should have training and expertise in the management of thyroid cancer and be a member of the MDT **(IV, C)**.

4 Pathology (section 12)

- i. Pathologists dealing with thyroid tumours should have expertise and interest in thyroid cytology and histopathology **(IV, C)**.
- ii. All patients should be staged by clinical and pathological TNM staging **(III, B)**.
- iii. Patients should be assigned to the appropriate risk group **(III, B)**. Low-risk patients are defined for the purpose of these guidelines, as those in the TNM stage I, who have a probability of long-term survival greater than 98%.

5 Radioiodine (¹³¹I) ablation / therapy and external beam radiotherapy (section 6)

- i. An oncologist (or nuclear medicine physician) with expertise and an interest in the management of differentiated thyroid cancer should supervise this treatment and be a member of the MDT **(IV, C)**.

- ii. Those administering therapeutic ^{131}I must hold an appropriate ARSAC certificate or must administer ^{131}I under the direction / supervision of an appropriate ARSAC certificate holder **(IV, C)**.
- iii. ^{131}I ablation / therapy should only be carried out in centres with appropriate facilities **(IV, C)**.

6 Aims of treatment

- i. Removal of all tumour
- ii. Elimination of clinical, radiological, or biochemical evidence of recurrence
- iii. Minimisation of unwanted effects of treatment

7 Summary of management of differentiated thyroid cancer

- i. All new patients should be seen by a member of the MDT, and the treatment plan should be discussed and endorsed by the MDT (section 2.5) **(IV, C)**.
- ii. Fine-needle aspiration cytology (FNAC) should be used in the planning of surgery (section 3) **(III, B)**.
- iii. Patients with papillary thyroid cancer (PTC) more than 1 cm in diameter or high risk follicular thyroid cancer (FTC) should undergo near-total or total thyroidectomy. Patients with low risk (section 1.4) FTC or PTC ≤ 1 cm may be treated with thyroid lobectomy alone (section 5.2) **(III, B)**.
- iv. Serum thyroglobulin (Tg) should be checked in all post-operative patients with differentiated thyroid cancer, but not sooner than 6 weeks after surgery (section 8.4) **(IV, C)**.
- v. Patients will normally start on triiodothyronine 20 mcg tds (normal adult dosage) after the operation. This should be stopped two weeks before ^{131}I ablation or therapy (section 6.1) **(IV, C)**.
- vi. The majority of patients with a tumour size of more than 1 cm in diameter, who have undergone a near-total / total thyroidectomy, should have ^{131}I ablation (section 5.2) **(III, B)**.
- vii. *Always exclude pregnancy and breast feeding before administering ^{131}I (section 6.1) (IV, C)*.
- viii. Breast feeding should be stopped at least 4 weeks and preferably 8 weeks before ^{131}I (section 6.1) and should not resume breastfeeding **(IV, C)**.
- ix. A post-ablation scan (3-10 days after ^{131}I ablation) should be performed (section 6.2) **(III, B)**.
- x. Patients treated with ^{131}I will require levothyroxine therapy in a dose sufficient to suppress the serum TSH to $< 0.1\text{mIU/l}$ **(III, B)**. Levothyroxine can be commenced 3 days after ^{131}I in a dose sufficient to suppress TSH to $< 0.1\text{mIU/L}$. In patients confirmed to be low-risk, a serum TSH $< 0.5\text{mIU/L}$ is probably acceptable (section 8.3).
- xi. Reassessment with a whole body scan (WBS) after stopping levothyroxine for 4 weeks, and stimulated serum Tg is indicated no earlier than 6 months after ^{131}I ablation. If abnormal uptake of the tracer is detectable, a ^{131}I therapy dose should be given and a post-treatment scan (3-10 days after ^{131}I therapy) should be performed. Following this the patient should restart levothyroxine (section 8.4 & 8.5) **(III, B)**.
- xii. In low risk (section 1.4) patients measurement of Tg after TSH stimulation alone (i.e. without a diagnostic ^{131}I whole body scan) may be adequate. In such cases ultrasonography of the neck 6-12 months after thyroidectomy is indicated (section 8.5) **(III, B)**.

- xiii. If there is suspicion of residual disease, further scans should be carried out, usually six months after ¹³¹I therapy (**IV, C**).
- xiv. External beam radiotherapy is only occasionally used, for patients with pT4 tumours (TNM staging) and presumed residual disease in the neck, which is not amenable to further surgery, particularly when the tumour does not take up ¹³¹I (section 7). External beam radiotherapy also has a role as a palliative measure in patients with advanced symptomatic local or distant disease (section 9).

8 Follow-up of differentiated thyroid cancer

This should be life-long (**IIb, B**) because:

- The disease has a long natural history
- Late recurrences are not rare, and can be treated successfully.
- Regular follow-up is necessary for monitoring of treatment (TSH suppression, the consequences of supraphysiological levothyroxine replacement, treatment of hypocalcaemia).
- **Life-long suppression** of serum TSH level below normal (<0.1mIU/L) is one of the main components of treatment in high risk cases (**III, B**).
- Patients should be monitored for late side effects of ¹³¹I treatment (**IV, C**).

Surveillance for recurrence of disease is essential and is based on:

- Annual clinical examination (**IV, C**).
- Annual measurement of serum Tg and TSH (**IV, C**).
- Diagnostic imaging and FNAC when indicated (**III, B**).

Support and counselling are necessary, particularly in relation to pregnancy (**IV, C**).

9 Medullary thyroid cancer (section 14)

- i. The initial evaluation of suspected medullary thyroid cancer (MTC) includes FNAC and measurement of plasma calcitonin (**III, B**).
- ii. The MDT should include or have access to a Clinical Genetics Service and *RET* gene testing (**IV, C**).
- iii. All patients with MTC should be offered genetic counselling and *RET* mutation analysis, whether or not there is an evident family history (**IV, C**).
- iv. *RET* mutation testing should include exons 10, 11, 13, 14, 15 and 16; screening of exons 10 and 11 alone is an incomplete test (**III, B**).
- v. Familial MTC represents 25% of all cases of MTC and associated endocrinopathies should be sought (MEN2A and 2B) (**IV, C**).
- vi. Pheochromocytoma and primary hyperparathyroidism should be excluded in new patients with MTC, by measuring 24 hour urine or plasma catecholamines and metanephrines and serum calcium (**IV, C**).
- vii. The minimum treatment is total thyroidectomy and level VI node dissection (**III, B**).
- viii. Prophylactic surgery should be considered in disease-free carriers of germ line *RET* mutations. Surgery should be performed in MEN2A patients before the age of 5 years (**III, B**). MTC occurs early in MEN2B and is particularly aggressive; thyroid surgery should be performed ideally by the age of 12 months. In children from FMTC kindred, surgery can be postponed until after 10 years of age.
- ix. Life-long follow-up is essential and includes monitoring of the tumour marker calcitonin (**III, B**).

1. Introduction

1.1 The need for guidelines

In spite of advances in diagnostic methods, surgical techniques, and clinical care, differences in survival of patients with thyroid cancer are evident in different countries and the outcome in the UK prior to 1989 appeared to be worse than other western European nations⁶. The reasons for this are unclear and may be multifactorial. It is hoped that the establishment of national guidelines for thyroid cancer, and their implementation through local protocols, would lead to better care, and subsequent improvement in survival for patients with thyroid cancer in England and Wales.

1.2 Aim of the guidelines

The intention is to provide guidance for all those who are involved in the management of patients with differentiated thyroid cancer. This document is not intended as a guideline for the investigation of thyroid nodules.

A summary of the key recommendations for the management of adult differentiated and medullary thyroid cancer is provided (previous section). Randomised trials are often not available in this setting. Therefore, evidence is based on large retrospective studies and the level of evidence according to AHCPR^{3,4} is largely II-IV.

The three main aims of the guidelines are:

- To improve the long-term overall and disease-free survival of patients with thyroid cancer
- To enhance the health-related quality of life of patients with thyroid cancer
- To improve the referral pattern and management of patients with thyroid cancer

1.3 Incidence

The incidence of thyroid cancer appears to be increasing slowly. In the period 1971-1995 the annual UK incidence was reported at 2.3 per 100,000 women and 0.9 per 100,000 men, with approximately 900 new cases and 250 deaths recorded in England and Wales due to thyroid cancer every year⁷. In 2001 data from Cancer Research UK showed 1200 new cases in England and Wales, with a reported annual incidence for the UK of 3.5 per 100,000 women and 1.3 per 100,000 men⁸. Thyroid cancer is the commonest malignant endocrine tumour, but represents only about 1% of all malignancies⁷.

1.4 Prognostic factors

The long-term outcome of patients treated effectively for differentiated thyroid cancer is usually favourable. The overall ten-year survival rate for middle aged adults with differentiated thyroid carcinoma is 80 - 90%. However, 5 - 20% of patients develop local or regional recurrences and 10 - 15% distant metastases. Nine percent of patients with a diagnosis of thyroid cancer die of their disease.⁹

It is important to assess risk in patients with DTC using a prognostic scoring system: this enables a more accurate prognosis to be given and the appropriate treatment decisions to be made. Any of the staging methodologies (TNM, AMES, MACIS, EORTC, AGES) can be used to assign patients to the high-risk or low-risk band, based on well-established prognostic factors (detailed below). TNM and MACIS probably yield the most useful prognostic information^{10,11}.

Low-risk patients are defined for the purpose of these guidelines as those in the TNM (5th edition)^{10,12} stage I category, who have a probability of long-term survival greater than 98%. The principal factors contributing to high-risk are older age, male gender, poorly differentiated histological features, tumour size, extrathyroidal invasion and metastatic spread. Treatment also influences prognosis¹³.

Age

Age at the time of diagnosis is one of the most consistent prognostic factors in patients with papillary and follicular thyroid cancer. The risk of recurrence and death increases with age, particularly after the age of 40 years¹³⁻¹⁸. Young children, under the age of 10 years, are at higher risk of recurrence than older children or adolescents^{19,20}.

Gender

The male gender has been reported as an independent risk factor in some but not all studies^{9,16,17,21}.

Histology

The prognosis of papillary thyroid cancer is better than follicular thyroid cancer, however if the confounding effects of age and extent of tumour at diagnosis are removed, survival rates are comparable^{13,16,22-24}. Within the papillary thyroid cancer group poorer prognosis is associated with specific histological types²⁵⁻²⁸ and the degree of cellular differentiation and vascular invasion^{14,29}. “Widely invasive” and “vascular invasion” are features of follicular cancers associated with a poorer prognosis^{28,30}. Poorly differentiated follicular cancers (insular carcinoma) and Hürthle cell carcinomas are also associated with a poorer outcome^{16,17,31}.

Tumour extent

The risk of recurrence and mortality correlates with the size of the primary tumour^{13,15-18,21,31}. Extrathyroidal invasion^{13,15-18,29,32,33}, lymph node metastases^{13,16,17,31}, and distant metastases^{32,34-36} are all important prognostic factors.

Prognostic scoring systems for differentiated thyroid cancer

Staging

The 5th edition of the TNM classification is recommended^{10,12,12a,12b} **(III, B)**. The MACIS scoring system is also useful in assessing risk²⁹.

The TNM system

Primary tumour

pT1	Intrathyroidal tumour, ≤ 1cm in greatest dimension
pT2	Intrathyroidal tumour, >1cm to 4cm in greatest dimension
pT3	Intrathyroidal tumour, > 4cm in greatest dimension
pT4	Tumour of any size, extending beyond thyroid capsule
pTX	Primary tumour cannot be assessed

Regional lymph nodes (cervical or upper mediastinal)

N0	No nodes involved
N1	Regional nodes involved If possible, subdivide
	N1a Ipsilateral cervical nodes
	N1b Bilateral, midline or contralateral cervical nodes or mediastinal nodes
NX	Nodes cannot be assessed

Distant metastases

M0	No distant metastases
M1	Distant metastases
MX	Distant metastases cannot be assessed

Papillary or follicular carcinoma

	<i>Under 45 years</i>	<i>45 years and older</i>
Stage I	Any T, any N, M0	pT1, N0, M0
Stage II	Any T, any N, M1	pT2, N0, M0
		pT3, N0, M0
Stage III		pT4, N0, M0
		Any pT, N1, M0
Stage IV		Any pT, any N, M1

Undifferentiated or anaplastic: all are Stage IV

<i>Stage</i>	<i>10 year cancer-specific mortality for differentiated (papillary or follicular) thyroid cancer¹⁰</i>
I	1.7%
II	15.8%
III	30%
IV	60.9%

MACIS scoring system

- 3.1 (if <38 years) or 0.08 x age (if >39 years)
- +0.3 x tumour size (in cm)
- +1 if incompletely resected
- +1 if locally invasive
- +3 if distant metastases present

<i>MACIS Score²⁹</i>	<i>20 year disease-specific mortality</i>
<6	1%
6-6.9	13%
7-7.9	44%
>8	76%

1.5 Public health and prevention

Nuclear fall-out is a well-recognised cause of an increase in the risk of thyroid cancer in children. Following the Chernobyl accident the incidence of thyroid cancer rose several hundred times in children in the region.

Therapeutic and diagnostic X-rays in childhood are also possible causes of thyroid cancer in adults, and limiting exposure to these sources should be undertaken whenever possible.

In cases of populations or individuals being contaminated with ¹³¹I, the thyroid can be protected by administering potassium iodide (http://www.arsac.org.uk/notes_for_guidance/index.htm)^{37,38}.

1.6 Screening

At present there is no screening programme to detect thyroid cancer for the general population..

Screening is possible for familial medullary thyroid cancers associated with specific oncogene mutations.

The genetic basis of papillary, follicular and anaplastic thyroid cancer has been investigated and, the roles and potential prognostic value of several genes e.g. RET, TRK, ras, BRAF and p53, identified. Testing for these genes is not routinely available in clinical practice.³⁹

The following are considered to be risk factors for thyroid cancer^{20,40-48}.

- History of neck irradiation in childhood
- Endemic goitre
- Hashimoto's thyroiditis (risk of lymphoma)
- Family or personal history of thyroid adenoma
- Cowden's syndrome (macrocephaly, mild learning difficulties, carpet-pile tongue, with benign or malignant breast disease)
- Familial adenomatous polyposis
- Familial thyroid cancer

While screening generally is not possible, a family history for thyroid cancer should be taken in each case and if there is a strong familial incidence of thyroid cancer, or association with other cancers, genetic advice should be considered in appropriate cases from the Regional Genetics Service **(IV, C)**.

2. Presentation, diagnosis and referral

Thyroid nodules are common in adults and may be detected by palpation in 10% of women and 2% of men⁴⁹. The prevalence may be as high as 50% or more if using sensitive imaging such as ultrasonography. The vast majority of thyroid nodules are benign and do not require urgent referral. Furthermore, thyroid cancer is uncommon in patients who are not euthyroid, and assessment of biochemical thyroid status is useful in deciding on the referral pathway by the primary care physician (See also section 16 – A Guide for the Primary Care Physician).

Cancer waiting times

Referrals for suspected cancer are required to be seen in secondary care within 2 weeks⁵⁰. Specialists in secondary care have a maximum of 31 days from ‘decision to treat’ to first definitive treatment and a maximum of two month (62 day) wait from urgent GP referral for suspected cancer to first definitive treatment (Figure 1).

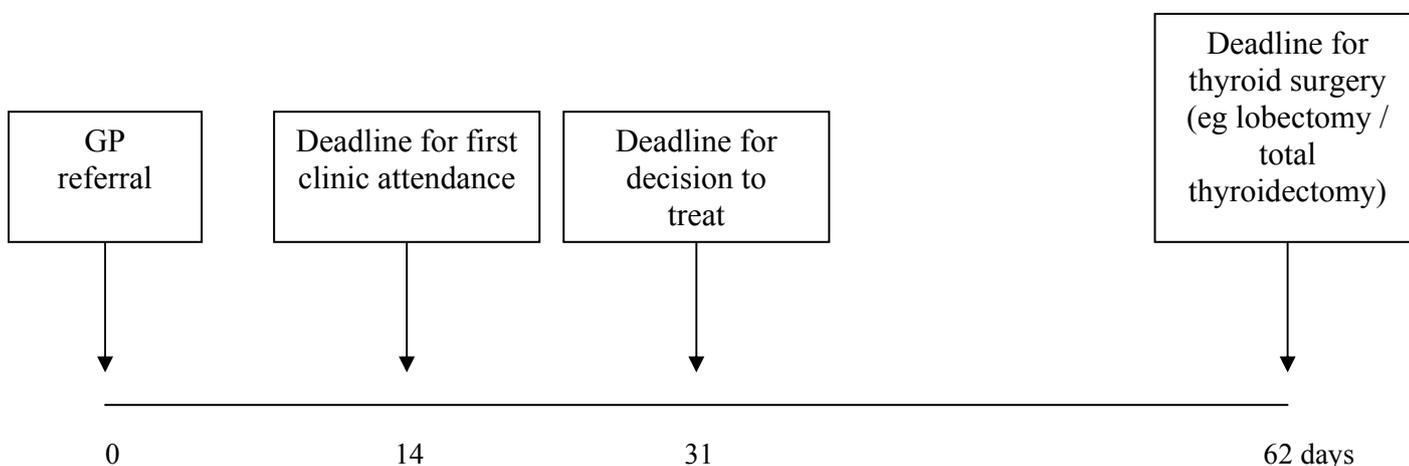


FIGURE 1

Cancer waiting times.

In the case of thyroid nodules, the time of ‘decision to treat’ is the time a decision to proceed to thyroidectomy is made on the basis of a cytology result of Thy 3, Thy 4 or Thy 5 (section 3). The date of first definitive treatment is the date of thyroidectomy (either lobectomy or total thyroidectomy).

The commonest presentation of thyroid cancer is a newly discovered palpable thyroid nodule or increase in size of a pre-existing nodule. However the vast majority of patients (95%) presenting in this manner have benign disease. Furthermore the prognosis in those who harbour a malignancy is generally excellent. ***The Thyroid Cancer Guidelines Update Group recommends that thyroid nodules need not be referred under the 2 week cancer rule unless there are suspicious clinical features (section 2.1) and that optimum care can be delivered by adopting a target of 4 weeks from referral to first assessment in secondary care, for the remaining cases (IV, C).***

Hospitals providing secondary care for patients with suspected thyroid cancer, should develop well defined and streamlined pathways of referral and care (**IV, C**). Appropriately resourced designated diagnostic clinics for patients with thyroid lumps are desirable.

2.1 Symptoms or signs that warrant investigation

Thyroid nodules and goitre are common and often noted coincidentally when patients are being imaged for other reasons. The vast majority (95%) of cases have benign disease. Primary care physicians must exercise common sense in selecting which cases should be referred and with what degree of urgency.

Patients with thyroid nodules who may be managed in primary care (IV, C):

- Patients with a history of a nodule or goitre which has not changed for years and in the absence of other worrying features (adult patient, no history of neck irradiation, no family history of thyroid cancer, no palpable cervical lymphadenopathy).
- Patients with a non-palpable asymptomatic nodule discovered coincidentally by imaging of the neck without other worrying features.

Patients that should be referred non-urgently (IV, C):

- Patients with nodules who have abnormal thyroid function tests (thyroid cancer is very rare in this group), should be referred to an endocrinologist
- Patients with a history of sudden onset of pain in a thyroid lump (likely to have bled into a benign thyroid cyst).
- Thyroid lump -newly presenting or increasing in size over months.

Symptoms needing urgent referral⁵⁰ (2 week rule) (IV, C):

- Unexplained hoarseness or voice changes associated with a goitre.
- Thyroid nodule in a child
- Cervical lymphadenopathy associated with a thyroid lump (usually deep cervical or supraclavicular region).
- A rapidly enlarging painless thyroid mass over a period of weeks (a rare presentation of thyroid cancer and usually associated with anaplastic thyroid cancer or thyroid lymphoma).

Symptoms needing immediate (same day) referral (IV, C):

- *Stridor* associated with a thyroid lump

2.2 Physical examination

The patient should have a full examination focussing on inspection and palpation of the neck, including the region of the thyroid, the deep cervical nodes and all other node groups in the neck, particularly the supraclavicular nodes. The pulse and blood pressure should be recorded (IV, C).

2.3 Appropriate investigations pending hospital appointment

- i. Thyroid function tests should be requested by the GP (IV, C).
- ii. Euthyroid patients with a thyroid nodule may have thyroid cancer and should be referred to a member of the Multi-Disciplinary Thyroid Cancer Team (section 2.4) (IV, C).
- iii. Patients with hyper- or hypothyroidism and a nodular goitre without suspicious features, should be referred routinely to an endocrinologist (IV, C).
- iv. Initiation of other investigations by the GP, such as ultrasonography or isotope scanning, is likely to result in unnecessary delay in making the diagnosis of cancer⁵² and is not recommended (IIb, B).

2.4 Who to refer to?

- i. Patients should be referred to a surgeon, endocrinologist, clinical oncologist or nuclear medicine physician who has a specialist interest in thyroid cancer and is a member of the MDT (see recommendation 1, Key Recommendations)¹ **(IV, C)**.
- ii. The local Cancer Centre or Cancer Unit⁵ should provide clear guidance on referral pathways to General Practitioners **(IV, C)**.

2.5 The role of the multidisciplinary team

All patients with differentiated thyroid cancer should be seen within a multidisciplinary team (MDT) framework as required by the NHS Cancer Services Standards^{1,51}.

- i. Patients will usually be seen initially by an individual member of the MDT, who will be working according to Guidelines **(IV, C)**.
- ii. The treatment plan and care of each newly diagnosed patient should be discussed and supervised by a core team (physician and surgeon) in consultation with other members of the MDT. This discussion should be recorded in the patient's records **(IV, C)**.
- iii. Close communication between members of the MDT is key for delivering optimal care and a combined clinic is the preferred format.
- iv. The management of MTC is best delivered by a dedicated group of clinicians within the MDT, with special expertise in this complex disease **(IV, C)**.

2.6 Hospital Investigations

Essential Assessments

- i. Thyroid Function Tests⁵² **(IIb, B)**
- ii. FNAC with or without ultrasound scan guidance^{53,54} **(IIb, B)**
- iii. Note that the measurement of serum Tg before thyroidectomy has no diagnostic or prognostic value and should not be undertaken⁵⁵ **(III, B)**.

Other assessments

A number of other investigations may be undertaken, but these are not routinely indicated.

- i. Thyroid autoantibodies may be measured if there is a suspicion of concurrent autoimmune thyroid disease (lymphoma of the thyroid occurs almost exclusively in the presence of Hashimoto's thyroiditis).
- ii. MR or CT scanning are indicated when the limits of the goitre cannot be determined clinically or for fixed tumours, or in patients with haemoptysis. It is important to avoid the use of iodinated contrast media when undertaking CT scans as these may reduce the subsequent radioiodine uptake by thyroid tissue. Gadolinium enhanced MRI may provide useful information without compromising subsequent radioiodine uptake by any remaining thyroid tissue. Ultrasound scanning is rarely diagnostic, but may be of value in aiding FNAC and in the evaluation of co-existing non-dominant nodules as well as any cervical lymphadenopathy⁵⁴.
- iii. Basal plasma calcitonin levels may be useful if MTC is suspected^{56,57} but is not recommended routinely for all thyroid nodules at present **(IV, C)**.
- iv. Flow-volume loop studies may be indicated if upper airways obstruction is suspected⁵⁸.

- v. Radioisotope studies are usually non-diagnostic for thyroid cancer and therefore of limited value particularly in iodine-replete countries^{59,60}.
- vi. Excisional biopsy is rarely indicated and when tissue diagnosis prior to intervention is difficult to obtain by FNAC, and would alter patient management (typically when lymphoma is suspected), core biopsy with or without ultrasound guidance is recommended **(IV, C)**.

2.7 Communicating the diagnosis

Informing the primary care team

- i. The GP should be informed (by telephone or fax) within 24 hours⁵¹ of the diagnosis of cancer being communicated to the patient for the first time, and should be made aware of the information which has been given to the patient and of the planned treatment **(IV, C)**.
- ii. Subsequently any alterations in prognosis, management or drug treatment should be communicated promptly **(IV, C)**.

Informing the patient

- i. The patient should be informed of the diagnosis of cancer by a member of the MDT; facilities should be available for this to be done during a private, uninterrupted consultation **(IV, C)**.
- ii. A trained nurse specialist should be available to provide additional counselling if required **(IV, C)**.
- iii. Whenever possible a relative or friend should attend the consultation and accompany the patient home **(IV, C)**.
- iv. Written information concerning thyroid cancer and its treatment and possible complications should be available to the patient (Appendix 5) **(IV, C)**.
- v. A prognosis should not be offered before adequate staging information is available **(IV, C)**.
- vi. Patients may have difficulty assimilating all this information at a single consultation and an opportunity for further explanation/discussion should be offered **(IV, C)**.

3. Fine needle aspiration cytology

3.1 Aspiration cytology of thyroid

The clinical usefulness of FNAC depends on obtaining adequate material for diagnosis, which requires close cooperation between biomedical scientists, pathologists and clinicians managing the patients so that appropriate procedures are set up, carried out and monitored.

- i. FNAC should be used in the planning of surgery⁷⁰⁻⁷² **(III, B)**. The diagnosis of thyroid malignancy should not be made by on FNAC alone. In many cases an operative procedure will be required to establish a diagnosis of malignancy. Ideally, procedures should be in place to allow adequacy of the sample to be assessed at the time of aspiration and for material to be retained for ancillary tests if necessary.
- ii. Thyroid cytology should be reported by a cytopathologist with a special interest in thyroid disease and should be a member of the MDT. There should be correlation between the cytological diagnosis and any subsequent histology **(IV, C)**.
- iii. Aspiration may be performed by a cytopathologist, endocrinologist, surgeon, nuclear medicine physician, oncologist or radiologist with expertise and interest in thyroid disease. However, he/she should be trained in good practice and should perform sufficient aspirates to maintain expertise and his/her performance should be monitored **(IV, C)**. FNAC can readily be carried out without ultrasound guidance if the lesion is palpable. In many centres there is a move towards the use of ultrasound guidance as this increases confidence that the lesion has been appropriately sampled. Care must be taken to avoid contamination of the samples with ultrasound gel when it is used.
- iv. All requests should include full clinical details and details of the aspiration procedure, including the site of the abnormality and the site of sampling **(IV, C)**.
- v. Where cysts are aspirated the pathologist should be informed whether or not there was complete resolution of the mass after aspiration. All the material aspirated (not just a sample) should be sent to the laboratory without fixation (and therefore without delay) as tumours may present as cysts **(IV, C)**. Any residual mass should be immediately reaspirated and the specimens identified separately **(IV, C)**. Cysts can be reported along the lines outlined below, but the stipulation regarding adequacy can be relaxed where a cyst aspirate has resulted in resolution of the mass.
- vi. The descriptive report will inform the clinical decisions on management, but many centres find it useful to add a numerical coding, such as that defined below (section 3.2). This helps both in guiding discussion on further management and in audit.
- vii. In some instances, particularly for the diagnosis of malignancy, ancillary tests are required to complete the cytological diagnosis. This requires appropriate material to be retained at the time of the FNA and is facilitated by the attendance of laboratory staff at the procedure. Immediate assessment of the cytology allows a decision whether immunocytochemistry, molecular analysis or flow cytometry is required. Liquid-based cytology is used in some labs but does not allow for either immediate assessment or flow cytometry and is not the preferred method for immunocytochemistry in all centres. Liquid-based cytology may be a useful adjunct to direct smears. Where appropriate, the results of additional investigations should be included in the text of the report. eg. immunopositivity for calcitonin in medullary carcinoma; immunocytochemistry, FACS analysis or molecular analysis of light chain (κ or λ) restriction in lymphoma **(IV, C)**.
- viii. FNAC can also be used in the diagnosis of suspicious lymph nodes (with the same requirements for assessing adequacy as for thyroid).
- ix. All cases with suspected or definitive diagnosis of neoplasia, or in whom there are discrepancies between clinical or radiological findings and cytology diagnosis should be discussed at the multidisciplinary meeting **(IV, C)**.

3.2 Diagnostic Categories

As noted in above (3.1 vi), these should only be used alongside the final cytology assessment after a text report.

Thy 1	-Non-diagnostic (inadequate or where technical artefact precludes interpretation; adequate smears usually contain six or more groups of greater than 10 thyroid follicular cells, but the balance between cellularity and colloid is more important).
<i>Action</i>	-FNAC should be repeated. Ultrasound guidance may permit more targeted sampling where the initial FNAC has been undertaken by palpation. Cysts containing colloid or histiocytes only, in the absence of epithelial cells, should be classified as Thy1 but should be clearly described as cysts. If the cyst has been aspirated to dryness with no residual mass, clinical/ultrasound follow up alone may be sufficient.
<hr/>	
Thy2	-Non-neoplastic (with the descriptive report documenting the features consistent with a colloid nodule or thyroiditis). Cysts may be classified as Thy2 if benign epithelial cells are present.
<i>Action</i>	-Two non-neoplastic results 3-6 months apart are generally advisable to exclude neoplasia ^{61,62} , however there are frequent cases where a reliable multi-disciplinary benign diagnosis can be achieved with a single well targetted aspirate. In high clinical risk group cases, the decision to proceed to lobectomy may be made even with a benign FNAC diagnosis.
<hr/>	
Thy3	(i) Follicular lesion / suspected follicular neoplasm. While some of these will be tumours, many will be shown to be hyperplastic nodules on surgical excision. The descriptive text will indicate the level of suspicion of neoplasia.
<i>Action</i>	Most of these patients should be treated by surgical removal of the lobe containing the nodule ^{61,62} (III, B) . Completion thyroidectomy may be necessary if the histology proves malignant. In some cases (based on clinical or radiological features) it will be more appropriate to observe if this decision is supported by the MDT.
	(ii) There may be a very small number of other cases where the cytological findings warrant inclusion in this category rather than Thy2 or Thy4 (eg. worrying features but cells too scanty to qualify for Thy4, repeat FNA advised). The text of the report should indicate the worrying findings (IV, C) .
<i>Action</i>	These cases should be discussed in the MDT to decide on the appropriate course of action (IV, C) .
<hr/>	
Thy4	Suspicious of malignancy (suspicious, but not diagnostic, of papillary, medullary, anaplastic carcinoma or lymphoma).
<i>Action</i>	Surgical intervention indicated for suspected cancer ^{61,62} (IIb, B) . Where Thy4 assessment has been given because of the absence of material for immunocytochemistry (medullary carcinoma) or flow cytometry (lymphoma), the aspirate should be repeated. These cases should be discussed at MDMs before deciding on management. (IV, B) .
<hr/>	
Thy5	Diagnostic of malignancy (unequivocal features of papillary, medullary, anaplastic carcinoma, lymphoma or metastatic tumour)
<i>Action</i>	The diagnosis should be discussed at the MDT meeting where further management should be agreed (IV, C) . Surgical intervention indicated for differentiated thyroid cancer and MTC ^{61,62} (IIb, B) , depending on tumour size, clinical stage and other risk factors such as gender and extremes of age. Indication for appropriate further investigation, radiotherapy and/or chemotherapy for anaplastic thyroid carcinoma, lymphoma, or metastatic tumour.

4. Primary treatment of differentiated thyroid cancer

4.1 Timescale

- i. Patients with suspected thyroid cancer should normally be seen within two weeks (section 2) **(IV, C)**.
- ii. If there are progressive/severe respiratory problems associated with a thyroid mass, patients must be referred and seen without delay **(IV, C)**.
- iii. Patients with new onset of stridor and a thyroid mass must be assessed as emergency cases **(IV, C)**.
- iv. Decisions should be made promptly with respect to diagnosis and treatment (maximum 31 days from diagnosis to first treatment and 62 days from urgent referral to first treatment (section 2, Figure 1) **(IV, C)**.
- v. ¹³¹I ablation should be offered within 3-8 weeks after surgery¹³ **(IV, C)**.

4.2 Staging and risk assignment

- i. Patients should be staged using the TNM classification (section 1.4), and assigned to the appropriate risk group (section 1.4) **(III, B)**.
- ii. Low-risk patients are defined in section 1.4.

4.3 Documentation

The following should be recorded in the notes **(IV, C)**:

- Family history
- Date of surgery
- Surgeon, assistant, anaesthetist
- Extent of surgery
- Complications of surgery
- The presence or absence of metastases including number and location of lymph nodes
- FNAC, histology and pTNM staging
- Curative or palliative intent
- Date of ¹³¹I ablation / therapy
- Dose of ¹³¹I ablation / therapy and side effects
- Follow-up arrangements

5. Surgery for differentiated thyroid cancer

The relationship between volume of thyroid surgery by individual surgeons and outcome is complex^{63,64}. However, there is a strong case for patients with thyroid cancer to be operated on and treated by clinicians who have appropriate training and experience.

The MDT will decide in consultation with the national bodies such as BATES, BAOHL-NS and specialist groups of the Royal Colleges, the TSG of the Cancer Network, who are to be the surgical and non-surgical specialists involved in the management of thyroid cancer **(IV, C)**.

A number of compliance measures recommended by the Manual of Cancer Services relate to thyroid cancer surgery and include a named surgeon to perform lymph node resection and complex surgical procedures to be performed in the same hospital of the MDM (<http://www.dh.gov.uk/assetRoot/04/13/55/91/04135591.pdf>).

Regular audit of outcomes and complications of surgery undertaken by the MDT will help clinicians to maintain their skill and professional development.

5.1 Preparation for surgery

- i. A hospital providing therapeutic surgery for patients with thyroid cancer should have a nominated surgeon who will be a member of the MDT with specific training in and experience of thyroid oncology¹ **(IV, C)**. Membership of the BATES, mandates annual returns and provides comparative performance data on surgical numbers and outcome measures.
- ii. Informed consent should be obtained from all patients after full discussion; the operating surgeon should normally obtain the consent **(IV, C)**.
- iii. The specific complications of thyroid surgery should be discussed as well as those complications which can occur in any surgical procedure; this should be recorded in the notes. Information sheets for the patient are recommended (Appendix 5) **(IV, C)**.
- iv. The use of prophylactic heparin preparations is not required for routine use in patients undergoing thyroid surgery **(IV,C)**. Thromboembolism prophylaxis should be used in all cases in the form of graduated compression hose (TED stockings) and peri-operative calf compression devices⁶⁵ **(Ia, A)**.
- v. In patients with suspected or proven thyroid cancer assessment of vocal cord function is strongly recommended prior to surgery⁶⁶ **(IV, C)**.
- vi. Pre-operative cross-sectional imaging with CT (without contrast) or MRI may be indicated if there is bulky disease or vocal cord paralysis⁶⁶.
- vii. Ultrasonography of the neck before thyroid surgery may be valuable in planning surgery, depending on individual surgeon's preference and availability of ultrasonographic expertise⁶⁷.

5.2 Elective surgical treatment for thyroid cancer

5.2.1 Thyroid surgery

The mainstay of treatment for DTC is surgery^{9, 13, 68-70}. Compliance with appropriate and clear definitions of surgical procedures is essential. A diagnostic thyroid FNAC (Thy 5) enables treatment to be planned and discussed with the patient prior to surgery⁷¹⁻⁷³.

- i. The following terms should be used **(IV, C)**:
 - a. Lobectomy: the complete removal of one thyroid lobe including the isthmus.

- b. Near-total lobectomy: a total lobectomy leaving behind only the smallest amount of thyroid tissue (significantly less than 1g) to protect the recurrent laryngeal nerves.
 - c. Near-total thyroidectomy: the complete removal of one thyroid lobe (lobectomy) with a near-total lobectomy on the contralateral side or, a bilateral near-total procedure. This should be clearly defined in the operation note.
 - d. Total thyroidectomy: the removal of both thyroid lobes, isthmus and pyramidal lobe
 - e. The terms “subtotal lobectomy” and “subtotal thyroidectomy” are imprecise and should be avoided. The classically described subtotal lobectomy or subtotal thyroidectomy procedures are inappropriate for the treatment of thyroid cancer. If a total thyroidectomy is not carried out the surgeon should document the exact extent of surgery to each lobe **(IV, C)**.
- ii. The recurrent laryngeal nerve/s should be identified and preserved in virtually all instances **(IV, C)**. Permanent damage to a recurrent laryngeal nerve should occur in significantly less than 5% of patients who have undergone surgery for thyroid cancer. Bilateral injuries are extremely rare. Nerve injury rates are higher after re-operative surgery⁷¹.
 - iii. Infiltration by tumour contributes to recurrent laryngeal nerve palsy rates in malignant disease. In benign disease and in small thyroid cancers (ie in the absence of recurrent laryngeal nerve infiltration) total thyroidectomy is associated with no higher risk of nerve injury than in lesser procedures, provided the nerves are identified⁷⁴.
 - iv. Attempts should be made to preserve the external branch of the superior laryngeal nerves by ligation of the superior thyroid vessels at the capsule of the gland **(IV, C)**. External laryngeal nerve injury has an associated morbidity, particularly in voice quality changes. Injury rates may be higher than for recurrent laryngeal nerve damage^{75,76}.
 - vi. Parathyroid glands should whenever possible be identified and preserved **(IV, C)**. If their vascular supply is compromised then the gland/s should be excised and reimplanted into muscle⁷⁷ **(III, B)**.
 - vi. Lymph node dissection in the central compartment (level VI) is associated with an increased risk of postoperative hypoparathyroidism^{78,79}.

5.2.2 Lymph Node Surgery

The following terms for lymph node groups and surgery should be used **(IV, C)**:

Lateral compartment of neck

- Levels I -Submental and submandibular nodes
- II -Deep cervical chain nodes from the skull base to the level of the hyoid. Further divided by their relationship to the accessory nerve - 2a (medial) and 2b (lateral)
- III -Deep cervical chain nodes from the level of the hyoid to the level of the cricoid.
- IV -Deep cervical chain nodes from the level of the cricoid to the suprasternal notch
- V -Posterior triangle nodes. Can be divided by their relationship to the omohyoid muscle into Va (above) and Vb (below)

Central compartment of neck

- Level VI -Pre and paratracheal nodes from the hyoid bone superiorly to the level of the sternal notch inferiorly, laterally to the carotid arteries.

Mediastinal nodes

- Level VII -Superior mediastinal nodes as far as the superior aspect of the brachiocephalic vein

Compartment 4⁸⁰

- Lymph nodes between the brachiocephalic vein and tracheal bifurcation within the anterior and posterior mediastinum

Selective neck dissection

Any type of cervical lymphadenectomy which involves less than dissection of levels I-V where the spinal accessory nerve (SAN), the internal jugular vein (IJV) and

sternocleidomastoid muscle (SCM) are preserved. The levels of node dissection should be clearly recorded.

Radical neck dissection

Radical neck dissections are very rarely indicated in the treatment of thyroid cancer but are defined here to ensure accuracy of nomenclature:

A classical ***radical neck dissection*** removes all of the lymphatic tissue in levels I-V along with the SAN, SCM and IJV.

Extended neck dissection is defined as removal of one or more additional lymph node groups such as parapharyngeal, superior mediastinal, and paratracheal nodes and / or non-lymphatic structures (digastric muscle, skin).

Modified radical neck dissection (MRND) involves removal of lymph nodes in levels 1 - V with preservation of one or more non lymphatic structures as follows:-

-*MRND Type I* - Excision of all lymph nodes routinely removed by radical neck dissection with preservation of the SAN.

-*MRND Type II* - Excision of all lymph nodes routinely removed by radical neck dissection with preservation of the SAN and IJV.

-*MRND Type III (Functional or comprehensive neck dissection)* -Excision of all lymph nodes routinely removed by radical neck dissection with preservation of the SAN, IJV, and SCM.

In most cases deciding on the type of surgery to be offered is straightforward and only requires endorsement by the MDT. In other complex cases the MDT must offer guidance on the basis of the individual patient's cytology and circumstances.

5.2.3 Surgery for papillary carcinoma

- i. Patients with a node negative cancer of 1 cm diameter or less (pT1, section 13.4) can be adequately treated by lobectomy followed by levothyroxine therapy (section 8.3)^{9, 60,64, 69,70,73} **(III, B)**.
- ii. For most patients, especially those with tumours greater than 1 cm, multifocal disease, extra-thyroidal spread, familial disease and those with clinically involved nodes, total thyroidectomy is indicated^{13,23} **(III, B)**. Total thyroidectomy is also indicated where there is a history of previous neck irradiation in childhood **(IV, C)**.
- iii. If the diagnosis of thyroid cancer has been made after thyroid lobectomy and completion (contralateral) thyroid lobectomy is required, the latter should be offered within 8 weeks of histological diagnosis of cancer **(IV, C)**.
- iv. Lobectomy alone may be appropriate treatment for some patients with tumours larger than 1 cm if the MDT judges that the risk of recurrence is low **(IV, C)**.
- v. In patients with clinically uninvolved nodes but deemed high-risk (ie any of the following features: male sex, age > 45 years, tumours greater than 4 cm in diameter, extracapsular or extrathyroidal disease), total thyroidectomy **and** level VI node dissection should be performed^{67,71} **(IV, C)**.
- vi. Palpable disease in level VI nodes discovered at surgery is treated by a level VI node dissection. When suspicious / clinically involved nodes are apparent preoperatively or are encountered at surgery in the lateral neck, and confirmed by needle biopsy or frozen section then a selective neck dissection (levels IIa-Vb) is recommended, preserving the accessory nerve, sternocleidomastoid muscle and internal jugular vein²⁸ **(IV, C)**.

5.2.4 Surgery for follicular carcinoma

- i. FNAC cannot at present distinguish follicular adenoma or benign hyperplastic nodules from carcinoma^{66,62,81} **(IV, C)**. Thy3 cytology usually mandates lobectomy as the least surgical procedure, although in some cases (identified by the descriptive report or by the specific clinical scenario) discussion at the MDT before deciding on an appropriate course of action may be indicated (section 3.1).
- ii. Frozen section examination is unhelpful when the FNAC diagnosis is that of a follicular lesion (Thy 3)⁸¹ **(IV, C)**.
- iii. If definitive histology reveals a follicular adenoma or a hyperplastic nodule, no further treatment is required **(III, B)**.
- iv. A follicular carcinoma under 1 cm with minimally invasive features should be treated by lobectomy (section 8.3)^{69,70,73} **(IV, C)**.
- iv. Patients with follicular cancer showing evidence of vascular invasion should be treated with total thyroidectomy **(IV, C)**.
- v. Patients with follicular carcinoma more than 4 cm in diameter should be treated with near-total or total thyroidectomy **(C)**.
- vi. Low risk patients (females patients <45 years of age) tumours measuring <2cm in size may be managed by lobectomy alone and levothyroxine therapy following MDT discussion and informed consent^{70,82,83} **(III, B)**.
- vii. Clear recommendations for otherwise low risk patients with tumours 2 - 4 cm cannot be made. Treatment should be at the discretion of the MDT.
- viii. Palpable / suspicious cervical lymph nodes are dealt with in a similar manner to papillary carcinoma (sections 5.2.3v, 5.2.3vi)^{9,13,70} **(IV, C)**.
- ix. If the diagnosis of thyroid cancer has been made after thyroid lobectomy and completion (contralateral) thyroid lobectomy is required, the latter should be offered within 8 weeks of histological diagnosis of cancer **(IV, C)**.

5.2.5 Surgery for oncocytic (Hürthle cell) carcinoma

Malignant Hürthle cell tumours (oncocytic or oxyphil) may behave more aggressively^{71,84}, than other histological types of differentiated thyroid cancer. Hürthle cell tumours are less likely to concentrate¹³¹I and total thyroidectomy should be considered.

5.2.6 Surgery for papillary or follicular microcarcinoma

Differentiated thyroid cancers which are less than 1 cm in diameter have an extremely low risk of death from thyroid cancer (0.1%)^{18,85,86} and can therefore be treated adequately by thyroid lobectomy **(III, B)** provided:

- They do not extend beyond the thyroid capsule
- There is no evidence of metastases
- There is no evidence of vascular invasion
- There is no evidence of multifocality
- There is no evidence of contralateral disease

5.3 Emergency surgery

It is rare for emergency surgery to be needed. Usually a careful work up of patients is achievable. Acute presentation of a patient with thyroid cancer and severe airway compromise requires urgent/immediate surgery **(IV, C)**.

5.4 Surgery for locally advanced disease

- i. When preoperative vocal cord examination has revealed no sign of recurrent laryngeal nerve involvement every attempt should be made to dissect the tumour from the nerve/s **(IV, C)**. In patients with unilateral nerve involvement associated with extensive extrathyroidal disease, the nerve may have to be sacrificed to achieve a curative procedure.
- ii. It may not be possible to remove the entire tumour without damaging both recurrent laryngeal nerves. A small residue of tumour may be left behind to protect the nerve/s and be subsequently dealt with by ¹³¹I ablation and TSH suppression with levothyroxine (section 8.3), with or without external beam radiotherapy (section 7)⁷⁴.
- iii. In individual patients with locally advanced disease involving the upper aero-digestive tract and/or one or both recurrent laryngeal nerves, curative excisional surgery of the tracheal wall and/or oesophagus should be considered **(IV, C)**.
- iv. When radical curative surgery is not possible or agreed to by the patient, treatment with radical radiotherapy and ¹³¹I should be considered **(IV, C)**.

5.5 Early post-surgical management of differentiated thyroid cancer

- i. After total / near-total thyroidectomy patients should be started on triiodothyronine **(IV, C)**. Normal adult dosage is triiodothyronine 20 mcg tds. This should be stopped for two weeks before either a radioiodine scan or ¹³¹I ablation of thyroid remnant **(IV, C)**.
- ii. Serum calcium should be checked within 24 hours of surgery. If hypocalcaemia is detected then it should be treated as indicated in section 8.2 **(III, B)**.
- iii. A baseline post-operative serum Tg should be checked, preferably no earlier than 6 weeks after surgery ^{55,87-91} **(III, B)**.

5.6 Medullary thyroid cancer

The management of medullary thyroid cancer is discussed in section 14.

5.7 Surgical Management of other rare malignancies of the thyroid

Thyroid lymphoma

Primary thyroid lymphomas occur on a background of Hashimoto's thyroiditis in the vast majority of cases.

- i. A clinical diagnosis or high index of suspicion of lymphoma should lead to FNAC and core biopsy.
- ii. Incision biopsy is not essential for the diagnosis of lymphoma ⁹² **(III, B)**.
- iii. Thyroidectomy is not indicated ⁹³ **(III, B)**.
- iv. The treatment of choice is chemotherapy followed by radiotherapy or radiotherapy alone. Most cases are high grade B cell lymphoma. Some are MALT (mucosa associated lymphoid tissue) tumours.
- v. Prognosis is generally excellent.
- vi. Patients should be referred to an MDT specialising in lymphoma management **(IV, C)**.

Anaplastic thyroid cancer

This has a very poor prognosis⁹⁴.

- i. Where the diagnosis has not been possible on FNAC, core biopsy may assist the diagnosis.
- ii. Surgery is rarely indicated. In a very small subgroup of cases chemo/radiotherapy and surgery may achieve a slightly longer period of survival⁹⁴⁻⁹⁶ **(III, B)**.
- iii. ¹³¹I ablation or therapy has no place **(III, B)**.
- iv. External beam radiotherapy is the mainstay of treatment with or without chemotherapy^{94,96} **(III, B)**.

6. Radioiodine ablation and therapy for differentiated thyroid cancer

Following a total or near-total thyroidectomy, some radioiodine uptake is usually demonstrable in the thyroid bed. ^{131}I destruction of this residual thyroid tissue is known as “radioiodine remnant ablation”. “Radioiodine therapy” refers to administration of ^{131}I with the intention to treat recurrent or metastatic disease. The principles and procedures are similar for the administration of ^{131}I for ablation or therapy purposes; the latter is discussed further in section 9.1.

6.1 Preparation for ^{131}I ablation or therapy

- i. The patient should be seen by an appropriate member of the MDT (ARSAC Certificate holder), preferably in a combined clinic (key recommendation 1 iii), for assessment and full discussion about radioiodine studies and treatment. Informed consent must be obtained from the patient before treatment **(IV, C)**.
- ii. Patients should adopt a low iodine diet for two weeks prior to ^{131}I and other sources of excess iodine should be eliminated (eg amiodarone therapy, or recent CT scan with contrast material), (Appendix 5, patient information leaflet 3) ⁹⁷⁻¹⁰⁰ **(III, B)**.
- iii. ^{131}I ablation and therapy must only be given in centres suitably equipped and certified for the purpose (www.ipem.org.uk/publications/IRR99.html) **(IV, C)**.
- iv. If ^{131}I can be administered within 3-4 weeks of thyroidectomy, no thyroid hormone replacement is required in the interim period. This would usually allow TSH to rise to >30 mIU/L at the time of ablation. For most centres however the interval between thyroidectomy and ^{131}I ablation will be longer. In these circumstances, patients should start triiodothyronine 20 mcg tds following surgery and this should be stopped 2 weeks before planned ablation to allow the serum TSH to rise >30 mIU/L **(IV, C)**.
- v. A pre-ablation scan is not indicated routinely. If there is doubt about completeness of surgery, a pre-ablation scan can be performed to assess remnant size. In such cases ^{123}I or $^{99\text{m}}\text{Tc}$ -pertechnetate may be preferable to ^{131}I , in order to reduce the risk of stunning ^{101,102}. Demonstration of large thyroid remnants should lead to consideration of further surgery before ^{131}I ablation ¹⁰³ **(III, B)**.
- vi. *Pregnancy must be excluded before ^{131}I ablation or therapy* **(IV, C)**.
- vii. Breast feeding must be discontinued at least 4 weeks and preferably 8 weeks before ^{131}I ablation or therapy **(IV, C)**. Breastfeeding should not resume.
- viii. Pre-treatment sperm banking should be considered in male patients likely to have more than two high dose ^{131}I therapy doses ^{104,105} **(IV, C)**. Adequate hydration at the time of treatment and for several days afterwards helps to prevent a decrease in sperm count.

6.2 Post-operative ^{131}I ablation

- i. The 2002 edition of this guideline recommended that most patients with differentiated thyroid cancer greater 1-1.5 cm in diameter, should receive ^{131}I ablation. This was based on several retrospective studies ^{13,32,36,106-108}, including a large cohort study with long follow up ¹³, which showed that patients older than 45 years with tumours > 1.5 cm had reduced local and distant recurrence and cancer death rates after remnant ^{131}I ablation. This recommendation **(III, IV, B, C)** remains largely valid, however recent evidence suggests that the benefit of ^{131}I ablation for low risk (section 1.4) patients may be questionable ^{109,110}.
- ii. Furthermore, recent data indicate that the incidence of a second malignancy after radioiodine might be higher than previously thought ^{111,112}. In the light of these findings the MDT decision about ^{131}I ablation should be individualised and selective **(IV, C)**.

- iii. Factors other than size of tumour (such as presence of metastases, completeness of excision, age, degree of invasion, associated co-morbidities) should be taken into account (IV, C).
- iv. Patients should be counselled so that they understand the rationale for ¹³¹I ablation (IV, C).

The benefits of ¹³¹I ablation include:

- Eradication of all thyroid cells including potential destruction of residual post-operative microscopic disease and thus possible reduced risk of local and distant tumour recurrence.
 - Reassurance to patients imparted by the knowledge that serum Tg is undetectable and iodine scan negative, implying that all thyroid tissue is destroyed.
 - Possible prolonged survival^{13,32}.
 - Increased sensitivity of monitoring by serum thyroglobulin measurements and possibly earlier detection of recurrent or metastatic disease^{9,113}.
- v. The acute and late side effects of radioiodine (also see section 6.4) should be discussed with the patient (IV, C), particularly stressing:
 - Moderate risk of a dry mouth and sialadenitis
 - Very small risk of second malignancies.
 - vi. Whenever possible the patient should make an informed decision based on the above risks and benefits (IV, C).

In the absence of randomised trials, recommendations on ¹³¹I ablation have to be based on retrospective studies^{1,13,32,36,107,108, 114} and recent consensus statements^{70,83}:

**A. No indication for ¹³¹I ablation (low risk of recurrence or cancer-specific mortality) (IV, C).
Patients should satisfy all of the criteria below for ¹³¹I ablation to be omitted.**

- Complete surgery.
- Favourable histology.
- Tumour unifocal, ≤ 1cm in diameter, N0, M0, or minimally invasive follicular thyroid cancers, without vascular invasion smaller than 2cm in diameter^{82,83}.
- No extension beyond the thyroid capsule.

B. Definite indications (IV, C).

Any of the following criteria constitute an indication for ¹³¹I ablation

- Distant metastases
- Incomplete tumour resection
- Complete tumour resection but high risk of recurrence or mortality (tumour extension beyond the thyroid capsule, or more than 10 involved lymph nodes and more than 3 lymph nodes with extracapsular spread¹¹³).

C. Probable indications (IV, C).

The list of indications below applies to patients that do not fall under categories A and B above. Any one of the following categories is a “probable” indication for ¹³¹I ablation.

- Less than total thyroidectomy (inferred from operation notes, or pathology report, or when an ultrasound scan or isotope scan show a significant post-operative thyroid remnant).
- Status of lymph nodes not assessed at surgery (section 5.2)

- Tumour size >1 cm and <4 cm
- Tumours <1 cm in diameter with unfavourable histology (tall-cell, columnar-cell or diffuse sclerosing papillary cancers, widely invasive or poorly differentiated follicular cancers)
- Multifocal tumours <1 cm: this is controversial ^{13,114}.

Activity of ¹³¹I for ablation

- The present recommendation for remnant ablation is 3.7 GBq pending the results of ongoing trials ^{115,116} **(III, B)**.
- For patients with known metastases, higher ¹³¹I activities (5-7.4 MBq) ¹¹⁷ are often used.

Procedure for remnant ablation with ¹³¹I

- Information leaflets (Appendix 5) and support from the specialist nurse should be provided **(IV, C)**.
- Serum TSH and Tg should be measured immediately prior to ¹³¹I administration **(IV, C)**.
- A pregnancy test must be performed where indicated, immediately prior to ¹³¹I administration and the result should be negative **(IV, C)**.
- The serum TSH should be greater than 30 mIU/L at the time of ablation (see 6.1.iv) **(IV, C)**.
- rhTSH has recently been licensed for use with remnant ablation after total or near-total thyroidectomy, based on a randomised controlled trial in low risk (section 1.4) patients ¹¹⁸. RhTSH may also be used for ablation in cases where thyroxine withdrawal is contraindicated or ineffective in raising the serum TSH. Discussion of such cases by the MDT is recommended **(IV, C)**. The protocol consists of 0.9 mg rhTSH administered intramuscularly on two consecutive days followed by 3.7GBq of ¹³¹I ablation 24 hours after the second rhTSH injection.

Aftercare following ¹³¹I ablation

- After admission for ¹³¹I ablation, ward procedures should be followed and the patient discharged only after Medical Physics assessment. Written advice about restricting the extent of contact between the patient and others should be handed to the patient before discharge **(IV, C)**. At the time of discharge (usually 3 days after ¹³¹I), thyroid hormone treatment (normally levothyroxine) should be commenced and a letter must go to the GP with the patient **(IV, C)**.
- A post-ablation scan should be performed 3-10 days after the ¹³¹I dose ¹¹⁹ **(III, B)**.
- Patients should be reviewed (preferably in a combined clinic) after 2-3 months for assessment, adjustment of TSH suppressive dose of levothyroxine, and to make arrangements for follow-up Tg measurement and scanning **(IV, C)**.

6.3 Diagnostic scan (¹³¹I 74 to 150 MBq) ^{98,120}

Indications for ¹³¹I diagnostic scan after ¹³¹I ablation

Diagnostic scans (see 6.3.3) are carried out in order to assess the effectiveness of ablation and requirement for further ¹³¹I therapy ¹²¹.

Recent data indicate that low risk (section 1.4) cases may be assessed adequately by measuring serum Tg (in the absence of Tg assay interference) under conditions of TSH stimulation, without the need for a radioiodine scan, which rarely provides additional helpful information in such cases¹²¹⁻¹²⁴. In low risk cases therefore the diagnostic scan may be omitted, although TSH stimulated serum Tg should be assessed. If a diagnostic scan is omitted, ultrasonography of the neck is a valuable alternative in assessing local recurrence (section 8.5).

A diagnostic radioiodine scan (in conjunction with stimulated serum Tg measurement) should be performed in all other cases¹²¹ **(III, B)**.

6.3.1 Indications for repeat diagnostic scans after radioiodine ablation

- i. Patients with high-risk disease and with Tg antibodies interfering with serum Tg measurements, may need additional radioiodine, ultrasound or other cross-sectional (eg CT or MRI) scans (section 8.5).
- ii. No further diagnostic radioiodine scans are required for other groups of patients, unless there are indications of disease progression, such as a rising serum Tg, clinical or radiological evidence of progression (section 8.5). In such cases scans should be performed after thyroid hormone withdrawal rather than rhTSH unless there are clear contraindications to thyroid hormone withdrawal (further discussed in section 8.5) **(III, B)**.

6.3.2 Precautions

- i. Pregnancy: ARSAC recommends a minimum period of 6 months before conception for females, as the absorbed dose to the foetus should not exceed 1mGy¹²⁵ **(III, C)**. If pregnancy is deferred for at least 6 months after high dose ¹³¹I ablation or therapy to the mother, there is no risk to fertility or normal pregnancy, though there is a slightly increased risk of miscarriage if pregnancy occurs within one year of high dose ¹³¹I¹²⁶⁻¹²⁹ **(III, B)**.
- ii. In males a 4 month period of avoidance of fathering a child is recommended¹²⁵ **(IV, C)**.

6.3.3 Timing of radioiodine diagnostic scans

Diagnostic radioiodine scans usually are scheduled not earlier than 6 months after ¹³¹I ablation. In selected cases (patients with aggressive disease), this should be brought forward to 4 months¹¹⁹ **(IV, C)**.

6.3.4 Procedure

- i. Before a diagnostic radioiodine scan, patients should switch from levothyroxine to triiodothyronine replacement (triiodothyronine 20 mcg tid). Levothyroxine is routinely stopped four weeks, and triiodothyronine two weeks before the diagnostic scan **(IV, C)**.
- ii. The serum TSH and Tg should be measured on the day of the diagnostic scan and before the tracer dose of radioiodine is administered. A serum TSH >30 mIU/L is essential for optimal imaging **(IV, C)**.
- iii. If abnormal uptake of the tracer is detectable, further ¹³¹I therapy (usually 3.7 - 5.5 GBq) should be given **(IV, C)**. A post-treatment scan should be performed 3-10 days later, as it is a significantly more sensitive procedure than a diagnostic radioiodine scan employing a small (74-150 MBq) activity of ¹³¹I¹¹⁹ (section 9), **(III, B)**.
- iv. Patients should restart levothyroxine when the scan has been reported and the report discussed with the patient. The dose of levothyroxine is the same as prior to the diagnostic scan. Levothyroxine should not be restarted earlier than 3 days after the diagnostic radioiodine scan. Caution should be exercised when recommencing levothyroxine in patients with vascular disease **(IV, C)**.

- v. A low iodine diet should be advised before diagnostic radioiodine scans (and ¹³¹I ablation or therapy) (section 6.1,iii and Appendix 5 patient information leaflet 3 (III, B)).
- vi. Patients should have access to the clinic, the ward where iodine treatment was given, specialist nurse or the clinician's secretary (IV, C).

6.4 Short-term and long-term side effects of ¹³¹I ablation and therapy

The main side-effect is transient hypothyroidism, unless rhTSH is used ^{118, 123,130} (section 6.2).

Possible early effects

- Abnormality of taste and sialadenitis minimised by good hydration.
- Nausea (minimised by antiemetics).
- Neck discomfort and swelling within a few days of radioiodine can occur rarely. It is more common when a large thyroid remnant is present. Simple analgesics should be tried initially. A short course of steroids may be necessary in severe cases.
- Radiation cystitis, radiation gastritis, bleeding into secondary deposits and oedema in cerebral secondary deposits are all extremely rare after administered activities of 3 GBq or less ^{100,104,113}.

Possible late effects

- Dry mouth and abnormal taste.
- Sialadenitis and lachrymal gland dysfunction.
- Lifetime incidence of leukaemia and second cancers is low, of the order of 0.5% ^{100, 131-133}. Of 3 cohort studies only 1 showed an increased but non-significant risk of leukaemia (relative risk about 2). The risk of leukaemia increases with a high cumulative dose (greater than 18.5 GBq) and with use of additional external beam radiotherapy. Patients who have high cumulative dose of ¹³¹I may also be more likely to develop second malignancies (for example bladder, and possibly colorectal, breast and salivary glands) ^{111, 112,131}. The total cumulative activity should therefore be kept as low as possible ^{106,107,131-136}.
- Radiation fibrosis can occur in patients who have had diffuse pulmonary metastatic disease and have received repeated doses of ¹³¹I ¹³⁶⁻¹³⁸.
- Increased risk of miscarriage may persist for up to 1 year after ¹³¹I ablation / therapy ¹²⁶⁻¹²⁹.
- Infertility in men ^{104,105}

7. External beam radiotherapy

Post operative adjuvant external beam radiotherapy is infrequently indicated for differentiated thyroid cancer. It probably reduces local recurrence in patients at high risk due to residual disease, where further surgery is not appropriate^{96,139,140}. Radiotherapy should be planned carefully, preferably using 3D conformal planning techniques, with appropriate precautions taken for prevention of radiation myelopathy,^{15,107,141,142, 143,144,145} **(III, B)**.

Intensity modulated radiotherapy (IMRT) may have advantages over conventionally planned radiotherapy when treating the thyroid bed and regional nodes. However an important consideration in the adjuvant setting, is that the use of intensity modulated radiotherapy with multiple fields can theoretically increase the risk of second malignancies in long term survivors¹⁴⁶.

7.1 Adjuvant external beam radiotherapy

The main indications for adjuvant radiotherapy are:

- i Gross evidence of local tumour invasion at surgery, presumed to have significant macro- or microscopic residual disease, particularly if the residual tumour fails to concentrate sufficient amounts of radioiodine.
- ii Extensive pT4 disease in patients older than 60 years of age with extensive extra nodal spread after optimal surgery, even in the absence of evident residual disease^{96,108,141,144-146}.

7.2 High dose external beam radiotherapy as part of primary treatment

Indicated for **(IV, C)**:

- i Unresectable tumours that do not concentrate radioactive iodine.
- ii Unresectable bulky tumours in addition to radioactive iodine treatment.

For palliative radiotherapy, see section 9.2.

8. Post-treatment follow-up

Routine follow-up includes clinical assessment of thyroid status and examination of the neck or other relevant systems. Abnormal masses in the neck or elsewhere should trigger further investigations including FNAC (IV, C).

8.1 Voice dysfunction

This may result if there is external laryngeal nerve and/or recurrent nerve injury.

- i. Voice dysfunction must be investigated if symptoms persist beyond two weeks after surgery (IV, C).
- ii. The patient should be referred to a specialist practitioner who is capable of carrying out direct and/or indirect laryngoscopy (IV, C).

8.2 Management of hypocalcaemia

- i. Serum calcium should be checked on the day after surgery, and daily until stable^{147,148} (III, B). A decline in serum calcium concentration in the first 24 hours after surgery is predictive of the need for calcium supplementation¹⁴⁹.
- ii. If hypocalcaemia develops, commence calcium supplementation at an initial dose of 500mg elemental calcium 3 times daily (III, B). The dose is adjusted as indicated by the response. Occasionally intravenous calcium gluconate may be required. Mild asymptomatic hypocalcaemia usually does not require treatment, although monitoring is indicated.
- iii. If hypocalcaemia does not improve, or worsens, introduce alfacalcidol (or calcitriol) (III, B).
- iv. Close monitoring of serum calcium is needed to prevent hypercalcaemia (IV, C).
- v. Monitoring of serum calcium should be supervised in the specialist clinic, with the assistance of the GP if appropriate (IV, C).
- vi. After total thyroidectomy, 30% of patients will need calcium supplementation with or without alfacalcidol. By three months less than 10% of patients will still require calcium supplementation¹⁵⁰.
- vii. Hypoparathyroidism is often transient and a predictor of this is an elevated (or upper normal range) serum PTH concentration at the time of the occurrence of hypocalcaemia¹⁵⁰. Thus, the majority of patients on calcitriol / alfacalcidol / calcium supplements can have this treatment withdrawn. Supplements should be slowly and gradually reduced and serum calcium monitored every few months until withdrawn and the eucalcaemia is restored. The combined effects of hypocalcaemia and hypothyroidism are poorly tolerated and calcitriol / alfacalcidol / calcium supplement withdrawal should take place during euthyroidism (IV, C).
- viii. If hypoparathyroidism is permanent, the lowest dose of supplements should be adjusted so as to maintain the serum calcium at the lower end of the normal range, while avoiding hypercalciuria. In stable cases annual measurement of serum calcium is recommended (IV, C).

8.3. Long-term suppression of serum thyrotrophin (TSH)

- i. Levothyroxine should be used in preference to triiodothyronine for long-term suppression¹⁵¹ (III, B).
- ii. The dose of levothyroxine should be sufficient to suppress the TSH to <0.1mIU/L¹⁵¹⁻¹⁵⁵ (III, B).
- iii. The dose of levothyroxine should be adjusted by 25 mcg (about every 6 weeks), until the serum TSH is <0.1 mIU/L (IV, C). To achieve this, most patients will require 175 or 200 mcg daily.

- iii In patients with low risk (section 1.4) differentiated thyroid cancer, there is some evidence that it may be adequate to keep the serum TSH to below the reference range in the absence of full TSH suppression (typically 0.1-0.5 mIU/L) **(III, B)**¹⁵¹⁻¹⁵⁵, but robust long-term data are not available.
- iv. Suppressive levothyroxine therapy is best supervised by a member of the MDT **(IV, C)**, although alternative arrangements may be appropriate in low risk cases (see section 10 v).
- v. The GP should be advised of the reason for this suppression and of the target serum TSH concentration **(IV, C)**.

8.4 Measurement of serum thyroglobulin (Tg) in long-term follow-up (Appendix 1)

Tg is secreted by both normal and cancerous thyroid cells. In patients who have not had a total thyroidectomy and ¹³¹I ablation, the interpretation of serum Tg measurements is limited by the inability to differentiate between tumour and thyroid remnant^{156,157}. Detectable serum Tg is highly suggestive of thyroid remnant, residual or recurrent tumour.

The cut-off serum Tg concentration beyond which recurrent / persistent disease is implied depends on several variables including the assay employed by each laboratory. Individual laboratories should advise clinicians on the significance of detectable serum Tg at low concentrations (Appendix 1) **(IV, C)**.

A serum Tg which is rising with time while on suppressive thyroxine therapy is highly suggestive of tumour recurrence or progression.

Endogenous antibodies to Tg (TgAb) and other unidentified factors may interfere with the measurement of serum Tg. Measurement of TgAb is valuable in interpreting the serum Tg result, although the absence of TgAb does not absolutely exclude the possibility of interference with the Tg assay. There is evidence that TgAb measurement may be of some value in monitoring patients with thyroid cancer¹⁵⁷.

- i. To ensure continuity in monitoring, clinicians should use the same laboratory and Tg assay on a long-term basis. Laboratories should not change methods without prior consultation with clinical users of the service **(IV, C)**.
- ii. TgAb should be measured by a quantitative method simultaneously with measurement of serum Tg. If TgAb are detectable, measurement should be repeated at regular (~6 monthly) intervals. If negative they should be measured at follow-up when Tg is measured⁵⁵ **(IV, C)**.
- iv. Samples should not be collected sooner than 6 weeks post-thyroidectomy, or ¹³¹I ablation / therapy^{55,156-161} **(III, C)**.
- v. There is normally no need to measure serum Tg more frequently than 3 monthly during routine follow-up; for patients in remission an annual check of serum Tg should be measured while on suppressive levothyroxine treatment. **(IV, C)**.
- vii. Since Tg release is TSH-dependent, serum TSH concentration should be determined concurrently to aid interpretation. The requesting clinician should indicate on the form whether the patient is on thyroid hormone therapy and the TSH result should be available to the laboratory performing the Tg assay **(IV, C)**.
- viii. There is no need for TSH stimulation if the basal serum Tg is already detectable.
- vii. Patients in whom the basal Tg remains persistently detectable (ie while on suppressive levothyroxine therapy), or rises with subsequent assessments, require further evaluation¹⁵⁷ **(III, B)**.
- viii. At routine follow-up most patients should have serum Tg measured while on TSH suppression **(IV, C)**.

TSH stimulated serum Tg measurement

The diagnostic sensitivity of serum Tg measurements is enhanced by an elevated serum TSH concentration (optimally by serum TSH > 30 mIU/L)^{156,157}. Tumour recurrence or progression can be detected earlier by detecting a raised serum Tg after TSH stimulation compared with measurement of Tg on suppressive thyroxine therapy. Tg should be measured when the serum TSH is more than 30 mIU/L (usually in conjunction with diagnostic radioiodine scans) **(IV, C)**.

In low risk (section 1.4) patients who have undetectable serum Tg while on suppressive thyroxine therapy, stimulated serum Tg measurement alone (ie without a concomitant WBS), represents adequate initial follow-up, provided there is no Tg assay interference^{70,122,124}. A concomitant WBS in such cases rarely adds valuable information, although ultrasonography of the neck may be indicated (section 8.5). If serum Tg is undetectable under TSH stimulation, then in low risk patients subsequent long-term follow-up by measurement of serum Tg under TSH suppression alone is sufficient^{70,122,124} **(III, B)**.

TSH stimulation can be achieved either by thyroid hormone withdrawal (aiming for a serum TSH >30mIU/L, section 6.3.4 for procedure), or by injections of rhTSH while the patient remains on suppressive thyroxine therapy. The latter is indicated in selected cases (see below).

- i. TSH-stimulated serum Tg measurements (with or without a radioiodine scan) may be performed 6-8 months after ¹³¹I ablation or therapy **(IV, C)**. A single undetectable TSH-stimulated serum Tg in the absence of assay interference, is highly predictive of no future recurrence provided the Tg can be measured reliably (ie absence of assay interference) in low risk (section 1.4) patients who have undergone total or near-total thyroidectomy and ¹³¹I ablation¹⁶². The role of neck ultrasonography in such cases is discussed in section 8.5.
- ii. The TSH-stimulated serum Tg may remain detectable at low concentrations after ¹³¹I ablation. This could be indicative of residual / recurrent cancer, but in the majority of cases signifies the presence of thyroid remnant. An expectant policy in low risk (section 1.4) cases is recommended with repeat TSH-stimulated Tg assessments at 6-12 month intervals **(IV, C)**. In many cases, repeat assessments will reveal a gradual decline in stimulated serum Tg to the point of no detection, when routine follow-up should be resumed.
- iii. Patients in whom the stimulated serum Tg remains persistently detectable or rises with subsequent assessments, require further evaluation (section 9.1) **(III, B)**

Recommendations for the use of rhTSH-stimulated Tg in routine follow-up

TSH-stimulation for measurement of serum Tg (or for WBS) can be achieved by thyroid hormone withdrawal or by administration of recombinant human TSH (rhTSH).

- i. The suitability of patients for rhTSH should be assessed by the MDT **(IV, C)**.
- ii. For the following group of patients rhTSH is the only possible or safe option for diagnostic purposes¹⁶³ and for ablation or therapy:
 - hypopituitarism
 - functional metastases causing suppression of serum TSH
 - severe ischaemic heart disease
 - previous history of psychiatric disturbance precipitated by hypothyroidism
 - advanced disease / frailty.
- iii. Patients should be informed about the advantages and disadvantages of this diagnostic method compared with conventional thyroid hormone withdrawal **(IV, C)**.

- iv. In patients known to have anti-Tg antibodies interfering with the Tg assay it is preferable to perform diagnostic radioiodine scans after thyroid hormone withdrawal, rather than with rhTSH as the Tg data may be impossible to interpret, and WBSs after thyroid hormone withdrawal are more sensitive than after rhTSH administration¹²³ **(III, B)**.
- v. rhTSH is known to cause a transient but significant rise in serum thyroid hormone concentrations if functioning thyroid tissue is present. Therefore, caution should be exercised in patients with large thyroid remnants **(IV, C)**.
- iv. rhTSH (two 0.9 mg doses) should be administered by deep IM injection on days 1 and 2 and serum Tg measured on day 5¹²³ **(Ib, A)**. Due consideration must be given to the practicalities of collecting, handling and analysis of radioactive samples and advice must be obtained from the relevant radiation, transport and health and safety authorities **(IV, C)**.
- v. rhTSH should not be used if basal (unstimulated) serum Tg is elevated or the patient is expected to have¹³¹I therapy **(IV, C)**.

8.5 Role of imaging by ultrasonography and whole body ¹³¹I scanning in routine follow-up

After total thyroidectomy and post-operative ¹³¹I ablation, diagnostic WBSs have relatively low sensitivity in detecting residual or recurrent disease, when compared with measurement of serum Tg^{122, 123, 124,164}. Evidence supporting a specific adjunctive role for ultrasonography (in addition to routine measurement of serum Tg), or its utility compared with other modes of follow-up, is presently scanty⁶⁷.

Ultrasonography is a sensitive method for detection of residual disease in the thyroid bed and metastatic disease in lymph nodes; its sensitivity is higher than neck palpation. This technique is used routinely during follow-up in some centres, especially outside the UK. Ultrasonography may uncommonly suggest the presence of disease in the absence of a rise in serum Tg and may indicate the site of disease in those with a raised serum Tg. Ultrasonography may have a particular role when serum Tg measurements are unreliable because of the presence of assay interference.

- i. A single diagnostic WBS performed 6-8 months (but not sooner than 6 months) after ¹³¹I ablation is generally indicated except in those with low risk (section 1.4) disease (see iii below). If this is negative, further WBS is not usually required, depending on results of monitoring by measurement of serum Tg¹²¹ **(III, B)**.
- ii. If rhTSH is used for WBS (see 8.4 for indications) the recommended protocol is as follows **(Ib, A)**¹²³:
 - rhTSH (0.9 mg) should be administered by deep IM injection on days 1 and 2
 - a tracing dose of ¹³¹I (approximately 150 MBq) should be given on day 3
 - the scan should be performed on day 5. A minimum of 30 minutes scanning time or a minimum of 140,000 counts per minute should be obtained
 - serum Tg is also measured on day 5.
- iii. Low risk patients (section 1.4), who have been shown to have undetectable stimulated serum Tg in the absence of assay interference, do not require routine diagnostic WBS during follow-up if the serum Tg on suppressive levothyroxine therapy remains undetectable. In such cases ultrasonography of the neck 6-12 months after thyroidectomy is indicated^{122, 123, 124,164} **(III, B)**.
- iv. Patients who are likely to require ¹³¹I therapy should have a WBS under conventional thyroid hormone withdrawal. This includes patients with detectable serum Tg, known thyroid remnant or known metastatic disease **(IV, C)**.

9. Recurrent / persistent differentiated thyroid cancer

Early detection of recurrent disease can lead to cure or certainly long-term survival, particularly if it is operable or takes up radioactive iodine^{9,13,69,70,87,106,113,142,143,165}. Distant metastases develop in 5-23% of patients with differentiated thyroid carcinoma, mainly in the lungs and bones.

Detection of abnormal masses in the neck or elsewhere should lead to FNAC and other appropriate investigations (IV, C).

9.1 Recurrence in the thyroid bed or cervical lymph nodes

Surgical re-exploration is the preferred method of management, usually followed by ¹³¹I therapy^{68,107} (III, B). Recurrent neck disease uncontrolled by surgery and ¹³¹I therapy is best treated by high dose palliative external beam radiotherapy (section 9.7). As patients are likely to survive for a significant period, radical external beam radiotherapy (doses 50 – 66Gy) is often necessary with a daily fractionation and meticulous radiotherapy planning techniques^{96,139}.

While the strategy outlined above is applicable in high risk cases, the efficacy of an aggressive approach in low risk cases where sensitive diagnostic techniques (high definition ultrasonography, stimulated serum thyroglobulin measurements) indicate very low volume disease in the neck, is less well established.

9.2 Metastatic disease involving lung and other soft tissue areas

These sites of metastases are usually not amenable to surgery and should be treated with ¹³¹I^{13,100,136,166,167} (III, B). If the tumour takes up radioiodine, long-term survival is possible. The preferred treatment is repeated doses of ¹³¹I; activities ranging from 3.7-10.1 GBq at 3-9 month intervals have been employed, with the usual being 5.5 GBq given every 4-6 months^{142,98,136,166,167}. Late side effects of ¹³¹I therapy are minimised if intervals between treatments are no less than 6-12 months. While empirical doses are generally used, dosimetric assessment has been also helpful in certain studies^{96,167-169}.

- Pulmonary fibrosis following treatment with ¹³¹I for diffuse pulmonary metastases has been reported rarely. It can be avoided or minimised by using a lung activity, which is less than 2.96GBq (80 mCi) 48 hours after administration¹⁶⁸.

There is no maximum limit to the cumulative ¹³¹I dose that can be given to patients with persistent disease¹³⁶. A normal blood count must be confirmed prior to each ¹³¹I therapy administration and impairment of renal function would demand a lower dose¹⁴² (IV, C).

A WBS 3-10 days after ¹³¹I administration provides better scintigraphic assessment of disease than a diagnostic scan and response to treatment although this has been questioned¹¹⁹.

9.3 Bone metastases

Extensive bony metastases are generally not curable by ¹³¹I therapy alone. For solitary or limited number of bony metastases that are not cured by ¹³¹I therapy, external beam radiotherapy with / without resection and / or embolisation should be considered in selected cases. External beam radiotherapy also has a very important role in the management of spinal cord compression for vertebral metastases in addition to surgery⁹⁶.

9.4 Cerebral metastases

External beam radiotherapy has an important palliative role in the management of cerebral metastases along with surgery if appropriate⁹⁶.

9.5 Other Metastatic sites

In selected cases when there are a limited number of metastases, metastasectomy or radiofrequency ablation may also be helpful.

9.6 Unknown metastatic sites

For patients with rising serum Tg (section 8.4) and a negative diagnostic radioiodine scan the following is recommended ¹⁷⁰ **(III, B)**:

- i. Ensure that the diagnostic ¹³¹I scan is truly negative rather than falsely positive Tg (eg suboptimal serum TSH elevation).
- ii. Ensure that the thyroglobulin measurement is reliable and that there is no interference particularly by heterophil antibodies ¹⁷¹.
- iii. Check for possible iodine contamination (eg amiodarone therapy, or recent CT scan with contrast material).

The management of patients with a rising serum Tg and negative diagnostic radioiodine scan needs to be tailored to the individual after discussion in the MDT. There are three potential approaches:

- a) No action until the patient becomes symptomatic.
- b) Additional investigations aiming to localise the disease recurrence and offer specific therapy.
- c) Empirical use of ¹³¹I therapy ^{9,170,172,173}.

If option (b) is judged to be appropriate the following investigations are recommended:

- i. Neck ultrasound (with or without FNAC), or cervico-mediastinal MRI scan should be performed, as the commonest sites of recurrence are the thyroid bed and cervical and mediastinal lymph nodes ^{124,164} **(III, B)**.
- ii. If (i) is negative, a CT scan of the lungs should be done to exclude micronodular lung metastases **(IV, C)**.
- iii. If (ii) is negative, then bony secondary deposits should be excluded, either by ^{99m}Tc bisphosphonate scan or, if indicated, other imaging agents like ^{99m}Tc MIBI **(IV, C)**.
- iv. If the above are all negative, consider scanning with ¹⁸FDG-PET, ²⁰¹Thallium or ^{99m}Tc Tetrofosmin, to exclude potentially operable disease. ¹⁸FDG-PET scanning has a higher sensitivity for detecting dedifferentiating recurrent disease but at present is only available in selected centres in the UK ¹⁷⁴⁻¹⁷⁸. Thyroxine withdrawal ¹⁷⁵ and rhTSH administration ¹⁷⁹ have been shown to increase the sensitivity of ¹⁸FDG-PET scan. Patients with positive ¹⁸FDG-PET scan have been shown to have a markedly reduced 3 year survival compared with ¹⁸FDG-PET scan negative patients ¹⁷⁴. ¹⁸FDG-PET scan may reveal recurrent disease, which is operable. If the recurrent disease is not operable then consideration should be given to high dose palliative external beam radiotherapy.
- v. ¹¹¹In Octreotide imaging may be positive in some Tg positive iodine scan negative patients ¹⁸⁰. Data for the use of therapy with radiolabelled somatostatin analogues in patients with Hürthle cell carcinoma and dedifferentiated papillary carcinoma are limited ¹⁸¹.
- vi. If all the above are still negative, therapeutic ¹³¹I may be considered if the Tg continues to rise. Other factors that should be considered in making this decision include the risk category of the patient and the rate of rise of the serum Tg concentration ¹⁸². In such cases a post-treatment scan (3-10 days after ¹³¹I therapy) should be included, as previously undetected metastases may then be visible. A recent metaanalysis of published studies confirms that 50% of post-therapy scans performed with 'blind' therapy will be positive and a fall in Tg levels will subsequently be observed in 60% of patients with positive post-therapy scans ¹⁷². The usual dose of ¹³¹I is 3-5.5 GBq. The decision to treat should be taken by the MDT with the full informed consent of patient and consideration of the potential risks and benefits of the treatment in the absence of prospective randomised studies ^{83,183} **(IV, C)**.

- vii. The combination of a positive diagnostic radioiodine scan and an undetectable serum Tg is very rare. In such cases the possibility of false positivity should be adequately explored before administering further ^{131}I therapy¹⁸⁴ **(III, B)**.

9.7 Palliative care

Palliative care is not necessary in the vast majority of patients with differentiated thyroid cancer because they are cured. However, in a very small proportion of patients with recurrent end-stage disease (and in patients with anaplastic thyroid cancer) specialist palliative care help would be necessary. A consultant in palliative medicine should liaise with the MDT and patients requiring palliative care patients should be referred early to the local palliative care team¹⁸⁵ **(IV, C)**.

High dose palliative external beam radiotherapy may be appropriate in good performance status patients with anticipated survival of greater than six months. External beam radiotherapy also has a role in palliation of symptoms from fungating lymph nodes, bleeding tumour, stridor, superior vena caval obstruction along and dysphagia.

Stridor and fear of choking are very distressing and can also be alleviated by pharmacological means, palliative surgery and counselling.

Palliative chemotherapy

Palliative chemotherapy may have a role in end-stage disease uncontrolled by surgery, ^{131}I therapy or external beam radiotherapy. The agents used are doxorubicin and cisplatin, but durable responses are uncommon^{186,187}. Chemotherapy should be used only in patients with progressive and symptomatic disease **(IV, C)**. Concurrent chemo/radiotherapy has been tried, particularly in anaplastic carcinoma, with some very short-term benefits^{68,134,188,189}. New treatments are coming on line based upon an emerging understanding of the pathobiology of the disease. Agents that target different pathways are being developed and evaluated in clinical trials, and it may be appropriate to offer a patient with advanced disease the opportunity of participating in such a trial.

10. Long-term follow-up of differentiated thyroid cancer

- i. Regular follow-up is necessary particularly for detection of early recurrence, initiation of appropriate treatment, TSH suppression and management of hypocalcaemia. This can be undertaken by a member of the MDT, working in a multidisciplinary setting and according to the established local guidelines **(IV, C)**.
- ii. Once the thyroid remnant has been ablated the frequency of attendance will be decided in each case individually: usually 3-6 monthly for the first 2 years, decreasing to 6-8 monthly for 3 years, and annually thereafter **(IV, C)**.
- iii. Support and counselling may be necessary, particularly for younger patients, and in relation to pregnancy.
- iv. Follow up should be life-long **(IV, C)** because:-
 - The disease has a long natural history.
 - Late recurrences can occur, which can be successfully treated with a view to cure or long term survival.
 - The consequences of supraphysiological levothyroxine replacement (such as atrial fibrillation and osteoporosis) need monitoring especially as the patient ages.
 - Late side effects of ¹³¹I treatment may develop, such as leukaemia or second tumours.
- v. Low-risk cases who have completed their treatment, shown to be free of disease at 5 years and are no longer judged to require TSH suppression, may be followed up in settings other than the multidisciplinary thyroid cancer clinic. This may include a nurse-led clinic or in primary care following agreement of well defined protocols and re-referral pathways.
- vi. At each visit the following tasks should be completed **(IV, C)**:
 - Patient history
 - Clinical examination
 - Assessment of adequacy of TSH suppression and of possible effects of thyrotoxicosis
 - Measurement of Tg as a marker of tumour recurrence. *Tg antibodies should be measured simultaneously with measurement of Tg⁵⁵.*
 - Measurement of serum calcium and PTH if indicated.

11. Pregnancy and thyroid cancer

11.1 Diagnosis of thyroid cancer in pregnancy

The management of thyroid cancer diagnosed during pregnancy requires careful consideration of risks to mother and foetus. However thyroid cancer discovered during pregnancy does not behave more aggressively than that diagnosed in a similar aged group of non-pregnant women. Women of childbearing age with thyroid cancer generally have a good prognosis, similar to that in non-pregnant women¹⁹⁰. Discussion of the case by the MDT, as well as counselling of the couple, are imperative **(IV, C)**.

Surgery is indicated, but evidence regarding the optimum timing is unclear. Thyroidectomy in the first trimester of pregnancy carries a high risk of abortion, but may be performed safely in the 2nd trimester. Alternatively surgery can be deferred until after delivery, provided that the tumour is monitored regularly (eg by ultrasound) and found to be reasonably stable. In cases of advanced or aggressive disease delays in treatment would be undesirable, and termination of pregnancy may (rarely) need to be considered.

¹³¹I ablation or therapy must be avoided in pregnancy. Suppressive thyroxine therapy is safe during pregnancy.

- i. A thyroid nodule presenting during pregnancy should be investigated by FNAC **(IV, C)**.
- ii. Radioiodine scans are contraindicated in pregnancy and breast-feeding **(IV, C)**.
- iii. If thyroid cancer is diagnosed or suspected, the following options should be considered **(IV, C)**:
 - Defer thyroidectomy, ¹³¹I studies and treatment until the post-partum period
 - Perform a thyroidectomy during the 2nd trimester of pregnancy, to be followed by suppressive doses of levothyroxine, but defer the ¹³¹I studies until the post-partum period
 - Termination of pregnancy followed by thyroidectomy and ¹³¹I studies and treatment (this option is very rarely necessary).

11.2 Pregnancy in the treated patient

- i. In accordance with ARSAC, it is recommended that women should defer conception for a minimum of 6 months and men for a period of 4 months following ¹³¹I ablation or therapy ¹²⁵ **(IV, C)**. A small risk of spontaneous abortion may persist for up to 1 year after high dose ¹³¹I ablation or therapy ^{126,127,128,131,190,191}. There is no risk of previous ¹³¹I ablation or therapy to the foetus, provided the recommendations are followed ^{128,191}.
- ii. Suppressive levothyroxine therapy should continue during pregnancy and to achieve this, the dose should be increased as soon as pregnancy is confirmed by approximately 25% ¹⁹² and further adjusted if necessary according to monitoring of thyroid function tests **(III, B)**.
- iii. The thyroid status should be checked by measurements of serum TSH and free thyroxine during each trimester to ensure that TSH remains suppressed, as levothyroxine requirements may increase during pregnancy ^{55,192} **(IIa, B)**.
- iv. For men there should be a minimum period of 4 months from ¹³¹I ablation or therapy before unprotected intercourse takes place ¹²⁵ **(IV, C)**.

12. Thyroid cancer in childhood

Differentiated thyroid cancer is rare in children. Children at particular risk are those previously exposed to radiotherapy to the head or neck. Thyroid nodules are more likely to be malignant in children than in adults so surgical excision may be appropriate even if findings from FNAC suggest benign disease. Thyroid cancer in children aged 10 years or less is more aggressive than in adults and risk of recurrence is higher^{193,197}.

- i. The general principles of management are similar to those in adults, however the managing team must include a paediatric endocrinologist, paediatric oncologist (or nuclear medicine physician) and nurse specialist or counsellor **(IV, C)**.
- ii. Total thyroidectomy followed by TSH suppression is recommended for most patients² **(IV, C)**.
- iii. Selective neck dissection is recommended for children with clinically positive neck nodes¹⁹⁵.
- iv. ¹³¹I ablation^{2,195-197} is recommended for all children particularly those aged under 10 years, but the decision about ¹³¹I ablation should be individually determined **(IV, C)**.
- v. Follow-up with serial serum Tg measurements should be life-long¹⁹⁸ **(III, B)**.

Guidelines for the management of differentiated and medullary thyroid cancer (MTC) in children can be found in reference 2.

MTC in children is discussed in section 14.

13. Pathology reporting, grading and staging of thyroid cancer

13.1 General principles

Pathologists dealing with thyroid tumours should have a special interest in thyroid pathology or participate in a network with the opportunity of pathology review **(IV, C)**.

- i. Cases should be handled and reported according to the minimum datasets of the Royal College of Pathologists (<http://www.rcpath.org/resources/pdf/ThyroidDatasetFeb06.pdf>) **(IV, C)**.
- ii. Many of the features affect staging and prognosis and may therefore influence clinical management decisions. A general approach to specimen handling is outlined below. Points specifically relating to medullary carcinoma are discussed in Section 14.
- iii. Most lesions should have had FNAC before surgery^{49, 69} **(III, B)** (section 3), so at least a differential diagnosis should be available.
- iv. Frozen section may be used to confirm the diagnosis of papillary carcinoma, but should not be used to differentiate follicular carcinoma from adenoma^{199, 200} **(Ib, A)**.
- v. In all cases, the blocks taken should be appropriate to make the diagnosis, and to assess the extent of invasion and the completeness of excision **(IV, C)**.
- vi. Follicular lesions that are not grossly invasive should be widely sampled at the interface between the tumour, the capsule and the normal gland to detect capsular or vascular invasion. Small lesions (≤ 30 mm in maximum dimension) should be processed in their entirety and 10 blocks should be taken from larger lesions^{30, 201} **(III, B, IV, C)**.
- vii. Lymph nodes should be carefully dissected, the numbers counted and locations noted if possible **(IV, C)**. Ipsilateral, midline and contralateral nodes should be documented separately **(IV, C)**. Formal neck dissections should be dealt with according to RCPATH protocols for head and neck cancers (<http://www.rcpath.org/resources/pdf/HeadNeckDatasetJun05.pdf>) **(IV, C)**.

13.2 Gross description (C)

The following features should be included:

- Nature of specimen
 - lobectomy - right or left; total/near-total or subtotal; +/- isthmus
 - thyroidectomy - total or near-total
 - weight and dimensions
- Description of lesion(s)
 - single or multifocal
 - solid or cystic
 - dimensions (of largest if multifocal)
 - encapsulated or not
 - confined to gland or invading adjacent structures
- Lymph nodes
 - site
 - number

- macroscopic involvement
- Presence or absence of parathyroid glands

13.3 Microscopic report (C)

Core data sets for all tumour types

- Type of carcinoma.
- Whether the tumour is a single lesion or is multifocal.
- Maximum dimension of carcinoma.
- Completeness of excision.
- Extension into extrathyroidal tissues (this defines the lesion as pT4).
- The presence and extent of any lymphatic/vascular invasion.
- The site and number of lymph nodes involved.

Additional points for histological subtypes

- Papillary** Typical or variant (specify)
- Follicular** Angioinvasive or capsule only
Minimally invasive or widely invasive
- Oncocytic (Hürthle cell) follicular carcinoma** (At least 75% Hürthle cells)
Report in same manner as follicular.

13.4 Pathological staging

- There are a number of classifications in current use for the staging of thyroid cancer²⁰². It is recommended that at present, pathological staging should be performed on the basis of TNM classification²⁰²⁻²⁰⁴ (**III, B**). This is easy to apply and has been shown in a number of studies to correlate with outcome^{10,196} (section 1.4).
- The recommended stratification for age at diagnosis as under 45 years or 45 years and over should be applied to papillary and follicular tumours (**IV, C**).
- In multifocal lesions, the largest is used for staging purposes (**IV, C**).

13.5 Staging protocol

See section 1.4.

13.6 Grading of tumours

- Papillary carcinomas should have their specific subtype documented (eg. classical, tall cell variant, etc) (**IV, C**).
- Histological grading of thyroid tumours is not commonly performed and is not included in RCPATH dataset. However, grading may provide useful additional prognostic information^{27,205}. It is therefore recommended that, where possible, a grade be assigned to the primary tumour as follows (**IV, C**):

- G1 Well differentiated
- G2 Moderately well differentiated
- G3 Poorly differentiated
- G4 Undifferentiated
- GX Grade cannot be assessed

For papillary tumours, a simple grading system based on a combination of marked nuclear atypia, tumour necrosis and vascular invasion has recently been proposed²⁰⁵. Grade 1 tumours have none of these features, Grade 2 one or more. For follicular tumours, the presence of an insular, solid or other less well-differentiated component in a predominantly follicular lesion would warrant Grade 2. Predominance of the dedifferentiated component would place the tumour in Grade 3.

14. Management of medullary thyroid cancer

MTC is a rare disease (it accounts for 5-10% of all thyroid cancers) that requires a dedicated, multidisciplinary regional service. All patients with MTC should be referred for surgical treatment to the Cancer Centre⁵ **(IV, C)**.

Developments in the molecular genetics of MTC have facilitated a rational framework for management. The use and interpretation of molecular diagnostics is difficult and requires careful application in individual patients and their families^{206,207}.

The biology of MTC has unique implications for the development and structure of clinical services and management of this unusual disease.

- i. 25% of MTC is familial, (MEN2A/MEN2B/FMTC) necessitating a comprehensive and integrated approach to both the patient and their family. The familial forms are inherited in an autosomal dominant manner.
- ii. When MTC arises as part of a familial syndrome, assessment and management of the other endocrine tumours is required.
- iii. Patients may survive for many years even with a significant tumour burden. This makes the risk/benefit decisions for additional intervention for persistent or recurrent disease difficult.
- iv. Clinical services for MTC should dovetail with those for MEN1 and MEN2, which require similar services and address common issues **(IV, C)**.

14.1 History

- i. MTC may present with a lump in the neck or metastasis, or dysphagia, or with the systemic effects that result from coincident secretion of calcitonin and other peptides (frequent loose stools and vasomotor flushing). Less commonly, adrenocorticotrophin (ACTH) is secreted.
- ii. The diagnosis may be made following fine needle aspiration (FNAC) of a thyroid nodule or lymph node, in the absence of previous clinical suspicion. Unsuspected MTC can be found at surgery.
- iii. In all cases, a comprehensive family history must be taken to include 1st and 2nd degree relatives to search for features of MTC or other endocrinopathies that may occur in individuals with MEN2. This includes a history of unexpected sudden death, which should raise the suspicion of occult pheochromocytoma^{208,209} **(IV, C)**.

14.2 Hospital investigation

Pre-operative investigations should include:

- i. A baseline value for calcitonin^{55,210,211} **(Appendix 1.ii) (III, B)**.
- ii. At least one 24 hour urine sample assayed for catecholamines and metanephrines to exclude pheochromocytoma and a serum calcium to exclude hyperparathyroidism^{211,212}. These tests should be performed in all MTC patients prior to neck surgery even in the absence of a positive family history or symptoms **(III, B)**.

- iii. *RET* mutation analysis to establish the possible genetic basis for the disease within an individual or kindred **(III, B)**.
- iv. A stimulation test with calcium/pentagastrin may be indicated to confirm a diagnosis of MTC pre-operatively in relatives of patients with familial MTC, to exclude the rare causes of false positive basal calcitonin elevation or when calcitonin levels are only mildly elevated (Appendix 1)^{55,213}.

Routine preoperative staging of MTC with US / CT / MRI (chest, thorax, abdomen) is not essential prior to first time intervention, as it does not alter the need for neck surgery. These investigations however may provide the surgeon with information to guide the extent of surgery in the central compartment of the neck and superior mediastinum.

14.3 Treatment

Prior to thyroid surgery all patients should be managed as described in Section 5.1.

Surgery^{206-208, 214-217}

The aims of first time surgical treatment of MTC are loco-regional control (the neck and superior mediastinum), and in some patients to obtain a biochemical as well as clinical cure.

- i. All patients with established MTC should undergo total thyroidectomy and central compartment node dissection with the inferior limit of the dissection being the brachiocephalic vein (levels VI and VII)²¹⁸ **(III, B)**.
- ii. Patients with pT2 – 4 tumours, or palpable lymph nodes in the central or lateral compartment should in addition undergo bilateral selective neck dissection of levels IIa – Vb²¹⁸ **(III, B)**.
- iii. In the absence of direct invasion, the sternomastoid muscle / the internal jugular vein / the accessory nerve should be conserved. Routine dissection of levels I, IIb and Va is not required unless there are palpable / suspicious nodes at these sites. The management of recurrent laryngeal nerve involvement by tumour is described in section 5. When there is strong suspicion or evidence of mediastinal node involvement below the brachiocephalic vein, the patient should be considered for further surgery **(IV, C)**. This will require a sternotomy²¹⁸.
- iv. Patients with distant metastases at presentation often have prolonged survival. Even in the presence of disseminated disease, surgery (total thyroidectomy and central compartment node dissection) should be considered to prevent subsequent compromise of the trachea, oesophagus and recurrent laryngeal nerves. These structures should be preserved whenever possible **(IV, C)**.
- iv. Prophylactic surgery should be offered to disease-free carriers of germ line *RET* mutations, identified by genetic screening programmes^{216,219-221} **(III, B)**. The possibility of future surgery should be discussed with parents before testing children **(IV, C)**.
- v. In ideal circumstances these patients would be expected to have C-cell hyperplasia (CCH) rather than MTC, but in many cases, by the time of presentation the transition from CCH to MTC will have occurred. It is important to distinguish the need for therapeutic surgery from prophylactic surgery. This will depend upon the genotype, the age of the patient and the basal calcitonin^{219,222,223}.
- vi. Children with MEN2B should undergo prophylactic thyroidectomy within the first year of life. Children with MEN2A should undergo prophylactic thyroidectomy before the age of 5^{206,221} **(III, B)**.
- vii. In children with MEN2A under the age of 10, it is probably unnecessary to perform lymph node dissection. In older children and those with MEN2B, central compartment lymphadenectomy should probably be performed at the time of thyroidectomy.
- viii. Gene carriers from FMTC kindred should undergo prophylactic thyroid surgery after the age of 10; lymph node dissection is not indicated before the age of 20 years²²² **(III, B)**.
- ix. Following surgery, voice dysfunction and hypocalcaemia should be managed as described in sections 8.1 and 8.2.

Investigation of persistent or increasing hypercalcaemia

Post-operative samples should be measured no earlier than 10 days after thyroidectomy^{55,224} **(III, B)**. Plasma calcitonin levels are most informative 6 months after surgery⁵⁵.

There is good evidence that meticulous initial surgery will reduce the risk of postoperative calcitonin elevation but high calcitonin levels after surgery are a common finding. This will depend upon the pre-operative basal calcitonin, the stage of the tumour at presentation and the adequacy of initial surgery^{225,226}.

True local recurrence is unusual after adequate initial surgery. When initial surgery was incomplete, re-operation on the neck (lymphadenectomy of the central and/or lateral compartments) with curative intent should be considered **(IV, C)**.

Mediastinal lymphadenectomy may be necessary when there is a strong suspicion of, or proven nodal disease at this site.

It is important to distinguish loco-regional, persistent / recurrent disease from distant micro- or macro metastases as the cause of an elevated calcitonin. Non-invasive imaging (chest and abdominal CT or MRI and cervical and/or abdominal ultrasound, bone scan should be performed **(IV, C)** but may not be helpful because of the morphological pattern of metastatic MTC in lung and liver (i.e. miliary disease). Laparoscopy²²⁷, selective arteriography²²⁸ will in some cases, identify occult hepatic metastases. Other less invasive options to detect metastatic MTC in patients with rising calcitonin and negative whole body CT or MRI, include Pentavalent ^{99m}Tc-DMSA, ¹³¹I-MIBG, ¹¹¹In-Octreotide and ¹⁸F-DG-PET scans. In general functional isotope studies are most likely to detect bulk disease.

Re-operative surgery in the neck and mediastinum should be considered even when there are known distant metastases to prevent the complications of large volume disease affecting the airway, oesophagus or laryngeal nerves **(IV, C)**.

Radiotherapy and chemotherapy

- i. Routine adjuvant external beam radiotherapy has not been shown to improve survival^{229,230} but may improve the relapse free rate if there is gross microscopic residual disease or extensive nodal disease^{166,230}.
- ii. Radiotherapy may control local symptoms in cases of inoperable or secondary disease.
- iii. Chemotherapy is generally ineffective, but may be tried for progressive and symptomatic disseminated disease^{96,186,187,230,231}.
- iv. Radiolabelled somatostatin analogue and / or ¹³¹I-MIBG therapy may be useful in a small number of cases²³³⁻²³⁵, but have not been evaluated in clinical trials. Alpha-interferon and other new drugs (tyrosine kinase inhibitors) may also have a role, however the evidence base is scanty at present.
- v. Genetic immunotherapy may be useful in the treatment of inoperable metastatic disease. The use of suicide gene therapy and tyrosine kinase inhibitors is under investigation^{236,237}.
- vi. Treatment with any of these modalities should preferably be within a clinical trial.

Palliative Care

- i. Medical therapy should concentrate on symptom control **(IV, C)**.
- ii. Gastrointestinal symptoms often respond well to symptomatic treatment (such as Lomotil and / or codeine phosphate). Somatostatin analogues are a possible alternative which may decrease tumour peptide release.

14.4 Follow-up

Lifelong follow-up is recommended (IV, C):

- i. Response to primary surgery can be assessed clinically, and by the measurement of serum calcitonin and tumour markers, usually 6 months after surgery⁵⁵ (IV, C).
- ii. The presence of an elevated but stable calcitonin level post-operatively may be managed conservatively, provided treatable disease has been excluded radiologically. Progressively rising levels should trigger imaging for further staging. In the absence of recurrent symptoms, appropriate follow-up intervals are 6 – 12 months (IV, C).

14.5 Pathology

The general principles for specimen handling and gross description outlined in sections 13.1 and 13.2 should apply also to cases of medullary carcinoma. However, in cases of intrathyroidal tumour, the whole specimen should be blocked. Where possible the upper third of the lobe(s) should be sampled and immunostained for calcitonin to identify C cell hyperplasia (IV, C).

Microscopic report

The general principles of section 13.3 apply. It is recommended that the diagnosis is confirmed by calcitonin immunoreactivity (IV, C).

The following features should also be noted (IV, C):

Presence of amyloid
C cell hyperplasia

Tumour staging

The staging protocols used in section 1.4 should be applied (IV, C). Age is not a prognostic factor in medullary thyroid cancer.

Medullary carcinoma

Stage I	pT1, N0, M0
Stage II	pT2, N0, M0 pT3, N0, M0 pT4, N0, M0
Stage III	Any pT, N1, M0
Stage IV	Any pT, any N, M1

14.6 Molecular genetics^{208,221, 238-247}

Summary

- i. It is important to recognise the heritable form of MTC because of the risk of other tumours in the individual and in the family. Early recognition and prophylactic surgery in MEN2 are effective in reducing both mortality and morbidity.
- ii. Approximately 25% of MTCs are hereditary, as part of the MEN2 / FMTC syndrome.
- iii. Lack of family history does not exclude heritable disease. The disease may not be apparent in relatives because of 'skipped' generations; or an isolated case may be the start of a new family.
- iv. Inherited MTC without other endocrinopathies also occurs. It is inherited in similar ways but tends to be more indolent than other forms of MTC²⁴⁸.
- v. Because of the rarity of MTC and the complexity of genetic investigation and management, cases should be managed by a specialist clinical service in close liaison with a Regional Genetics Centre (IV, C).

Genetic investigation of a patient with MTC.

1 Clinical history suggestive of MEN2 syndrome:

Symptoms/history of pheochromocytoma, parathyroid disease.

Features of MEN2B: facies (see Appendix 2), constipation/diarrhoea, presence of mucosal neuromas, medullated corneal nerve fibres, marfanoid habitus, colonic ganglioneuromatosis.

Hirschsprung's disease (occasionally associated with MEN2).

A systematic family history should be taken, to include all first and second degree relatives, with attention to features suggestive of MEN2 (thyroid, adrenal, parathyroid disease) **(IV, C)**.

The history must be recorded in the case notes **(IV, C)**.

2 Genetic testing

Before testing:

- i. If expertise is not available within the primary clinical team, the patient should be referred to the Clinical Genetics Service **(IV, C)**.
- ii. Because of the possibility of heritable disease, every case of MTC should be offered genetic testing unless there are good reasons for not undertaking this. **(IV, C)**.
- iii. Testing should always begin with the affected individual, if he/she is available **(IV, C)**.
- iv. If the affected individual is not available, the decision and strategy for testing should be discussed with the Clinical Genetics Service **(IV, C)**.
- v. Before blood is taken, a clear explanation must be given of the nature of the test, the possible outcomes, and of the implications of a positive or negative result for the individual and the family. This explanation should be recorded in the case notes for each individual **(IV, C)**.

Testing:

- i. From the affected individual: ideally 10ml EDTA anticoagulated blood. Tests can be performed on smaller (e.g. 1 to 2ml) amounts of blood, but discuss this with the appropriate NHS genetics laboratory.
- ii. Send with clinical details and family history to appropriate NHS genetics laboratory.
- iii. Patients with no special clinical features should be tested first for *RET* mutations in exons 10 and 11; if these are negative, for exons 13-16²⁴³⁻²⁴⁷ **(III, B)**. Failure to screen exons 13-16 is an incomplete test.
- iv. Patients with clinical features of MEN2B should be tested first for mutations in codons 918 and 922 (exon 16), 883 (exon 15) and 804 and 806 (exon 14) **(IV, C)**.
- v. Patients with clinical features of Hirschsprung's should be tested first for mutations in codons 609, 611, 618, 620 (exon 10) **(IV, C)**.

Action on results:

If a mutation is found

- i. The result should be communicated, in the clinic, to the patient **(IV, C)**.
- ii. Permission must be obtained from the patient to disclose this result to anyone else, including GP and family **(IV, C)**.
- iii. A plan should be made for the management of the individual and for the further investigation of the family **(IV, C)**.
- iv. *The individual*
Mutation implies MEN2 and thus (depending on the site of the mutation) a future risk of other MEN2 components such as further thyroid tumours, adrenal and parathyroid disease.

- v. *The family*
Family members at risk should be offered testing for the specific *RET* mutation (IV, C).
- vi. Contacting and investigating the family requires expertise and coordination and should normally be undertaken by a specialist clinical genetics department, in liaison with the relevant clinical teams (IV, C).

If no mutation is found

- i. Check with the genetics laboratory that a complete mutation screen has been carried out, to include exons 10, 11 and 13-16 of the *RET* gene. If not, ask for this to be completed (IV, C).
- ii. If there is strong presumptive evidence from individual or family history of inherited disease:
 - a) discuss further with clinical genetics department and consider research-based search for novel mutations (IV, C).
 - b) consider biochemical screening of family members at risk using stimulated (I.V. calcium / pentagastrin, Appendix 1) calcitonin testing from age 5 years.
- iii. If there is no clinical evidence to suggest inherited disease, the need for stimulated calcitonin screening of family members at risk is unclear. There are a few MEN2 families (mostly with familial MTC only) in which *RET* mutations have not so far been identified. Thus, a failure to find a *RET* mutation in an isolated case of MTC cannot completely exclude the possibility of heritable disease. The extent of the remaining risk is very small – around 1% or less, depending on the clinical features of the patient. Young age at onset of the MTC (<35 years) and the presence of C-cell hyperplasia in the thyroid are in favour of inherited disease, but not conclusive; nor does absence of these features exclude it. The correct action in this situation is a matter for clinical judgement and may differ from family to family.

Mutation testing of tumour

- i. If no blood sample is available from the affected individual, DNA may be obtainable from either frozen or paraffin embedded tumour.
- ii. Interpretation of *RET* mutations identified from tumour tissue requires care. The mutations may be either germline or somatic in origin. Specialist genetic advice should be sought (IV, C).
- iii. A somatic MEN2B-type (codon 918) mutation is commonly present in sporadic tumours, but may also be present in tumours from MEN2A cases. This finding cannot therefore be used to exclude heritable disease.

14.7 MEN2B

Recognition:

Photographs to aid diagnosis will be found in Appendix 2. MTC occurs early in MEN2B and is particularly aggressive^{211,249}.

- i. Any new patient with MTC, especially a child or young adult, should be carefully assessed for clinical features suggestive of MEN2B^{198,209,250,251} (III, B).
- ii. The clinical features of MEN2B may be hard to recognise, and is sometimes diagnosed in error.
- iii. >98% of MEN2B patients reported to date have mutations in either *RET* codon 918 (95%) or 883 (3%). Unless the clinical evidence is strong, preferably with radiological and/or biopsy support, the absence of these mutations excludes MEN2B with high probability. Where there is doubt the patient should be referred for a specialist opinion^{251,252} (IV, C).

Child of an MEN2B patient

- i. Because MEN2B can present with clinically significant MTC in the neonatal period, management of the newborn child of a known MEN2B carrier should be planned in advance with specialist advice **(IV, C)**.
- ii. Because MTC occurs early in MEN2B and is particularly aggressive, thyroid surgery in an affected child should be done as early as possible, and preferably before the age of 12 months ²²¹ **(III, B)**.
- iii. Prenatal testing is possible. Couples who ask about prenatal testing for MEN2 should be referred to a genetics clinic **(IV, C)**.

15. Registration, core dataset and audit

It is mandatory for all patients with thyroid cancer in England and Wales to be registered within the Regional Cancer Network.

Further information on core dataset can be found on:

<http://www.icservices.nhs.uk/cancer/pages/dataset/thyroid.asp>

Prospective data collection and regular audit of outcomes and processes should be carried out **(IV, C)**.

The primary purpose is to ensure that all patients are adequately followed up.

The development of a national dataset will allow audit of national outcomes and will provide the potential for prospective assessment of different treatment modalities. This comprises a thyroid cancer specific dataset which has been in use at one hospital for the past decade and has undergone serial modifications during that time. This could be implemented for general use immediately to record treatment and relapse, and to facilitate audit. Subsequent analysis would then permit improvements in treatment and also setting up of prospective clinical trials. The NHS Information Authority is developing a generic data set for all cancers; this is available on the internet and will soon become established.

The proformas should be completed by a member of the MDT **(IV, C)**.

16. Thyroid cancer: a guide for the primary care physician

16.1 Raising awareness

- i. Thyroid nodules, particularly when solitary and clinically obvious should be investigated, as they carry a small but significant malignant potential (about 10% or less).
- ii. Cancer of the thyroid is rare representing only about 1% of all cancers.
- iii. The overall 10-year survival rate for differentiated thyroid carcinoma is 80 - 90%.
- iv. 5 - 20% of patients develop local or regional recurrences and 10 - 15% develop distant metastases.

16.2 Prevention

- i. Previous head or neck irradiation in childhood is a possible cause of thyroid cancer in adults. Exposure to radiation should be limited whenever possible.
- ii. Nuclear fall-out is a well recognised cause of increased risk of thyroid cancer.
- iii. In cases of populations or individuals being contaminated with radioactive iodine, the thyroid can be protected by administering potassium iodide^{254,255}.

16.3 Screening

General screening – no screening is indicated for the general population.

Risk-directed screening should be considered (by referral to the specialist secondary team) when the primary care physician identifies patients with:

- Familial thyroid cancer, including medullary thyroid cancer (MTC)
- History of neck irradiation in childhood
- Family history of multiple endocrine neoplasia type 2 (MEN2)

The following carry a statistically increased risk of thyroid malignancy but no screening is recommended:

- Endemic goitre
- Hashimoto's thyroiditis (risk of lymphoma)
- Family or personal history of thyroid adenoma
- Cowden's syndrome (macrocephaly, mild learning difficulties, carpet-pile tongue, with benign or malignant breast disease)
- Familial adenomatous polyposis

16.4 Diagnosis and referral

The usual presentation is that of a palpable lump in the neck, which moves on swallowing. There may be no other symptoms or signs.

Immediate (same day) referrals

Patients with stridor associated with a thyroid swelling should be referred immediately to secondary care (depending on locally provided facilities this may be the Accident and Emergency Department, Head and Neck or General Surgical emergency services).

Urgent referrals under the 2 week rule for suspected cancer

The presence of the following symptoms or signs in association with a thyroid swelling may indicate more aggressive or advanced disease and should be referred urgently under the 2 week rule:

- Unexplained hoarseness or voice change
- Thyroid nodule / goitre in a child
- Cervical lymphadenopathy associated with a thyroid lump (usually deep cervical or supraclavicular region).
- A rapidly enlarging painless thyroid mass over a period of weeks (a rare presentation of thyroid cancer and usually associated with anaplastic thyroid cancer or thyroid lymphoma).

Patients in whom exclusion of thyroid cancer is required, should be referred to a thyroid nodule clinic, or a surgeon, endocrinologist or nuclear medicine physician who has a specialist interest in thyroid cancer and is a member of the Regional Thyroid Cancer MDT.

Non-urgent referrals

- Patients with nodules who have abnormal thyroid function tests (thyroid cancer is very rare in this group), who should be referred to an endocrinologist
- Patients with a history of sudden onset of pain in a thyroid lump (likely to have bled into a benign thyroid cyst).
- Thyroid lump -newly presenting or increasing in size over months.

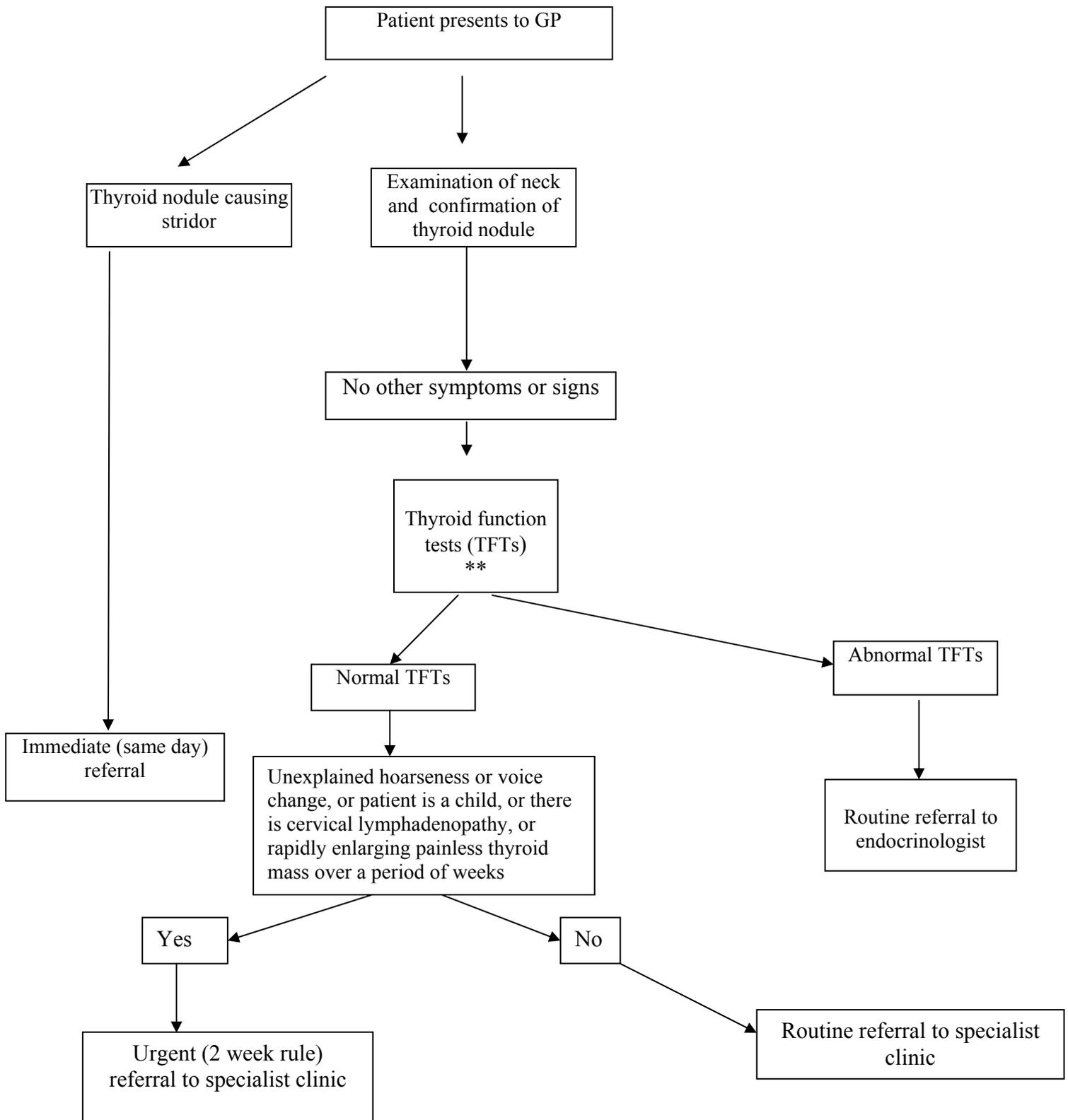
Physical Examination

- i. Examination focusing on inspection and palpation of the thyroid and neck, movement of the nodule with swallowing, and palpation of the deep cervical nodes and all other node groups in the neck especially supraclavicular nodes.
- ii. Pulse and blood pressure

Appropriate investigations pending hospital appointment

- i. Thyroid function tests should be requested by the GP and appended to the referral letter. Hyper- or hypo – thyroidism associated with a nodular goitre is unlikely to be thyroid cancer; these patients should be referred routinely to an endocrinologist.
- ii. Initiation of other investigations (such as ultrasound scanning or autoantibodies) by the primary care physician are unnecessary and may cause delay in making the diagnosis of cancer.

16.5 Algorithm for diagnosis & management of a thyroid nodule or suspected thyroid cancer in general practice



**** There is no need to arrange ultrasound of thyroid**

Communicating the diagnosis

Informing the primary care team

- i. The GP should be informed within 24 hours (by telephone or fax) of the diagnosis being communicated to the patient for the first time and should be made aware of the information which has been given to the patient and of the planned treatment.
- ii. Subsequent alterations in prognosis, management or drug treatment should be communicated promptly.

Informing the patient

- i. The patient should be informed of the diagnosis by a member of the specialist team.
- ii. A trained nurse specialist should be available in the specialist clinic to provide additional counselling if required.
- iii. Whenever possible a relative or friend should attend the hospital consultation and accompany the patient home.
- iv. Written information concerning thyroid cancer and its treatment should be available to the patient in the specialist clinic.
- v. A prognosis will not be offered before adequate staging information is available.
- vi. Patients may have difficulty understanding all this information at a single consultation and an opportunity for further explanation/discussion will be offered.

Summary of treatment of thyroid cancer

Treatment decisions will be made by the Thyroid Cancer MDT, who will continue to supervise the patient's care.

- i. Patients will commonly undergo thyroidectomy, followed in some cases by an ablative dose of radioiodine (^{131}I).
- ii. Thereafter patients will generally require thyroxine to suppress TSH to <0.1 mu/l, and some will need treatment to correct hypocalcaemia.
- iii. Scans and/or measurement of serum thyroglobulin (Tg) will be performed at regular intervals to detect possible recurrence.
- iv. Patients will be provided with written and verbal information about the disease and its management.
- v. Pregnancy: radioiodine is not given to pregnant patients. Pregnancy **must** be avoided for 6 months after ^{131}I ablation or therapy in women and 4 months in men. Breastfeeding needs to be stopped at least 4 weeks and preferably 8 weeks before radioiodine ablation or therapy and not be resumed.

16.6 Follow up

Follow-up of patients with thyroid cancer is life-long and usually supervised by specialists in secondary or tertiary care, who are members of the MDT. Low-risk cases who have completed their

treatment, shown to be free of disease at 5 years and no longer judged to require TSH suppression, may be followed up in settings other than the multi-disciplinary thyroid cancer clinic. This may be a nurse led clinic or in primary care following agreement of well defined protocols and re-referral pathways.

- i. ***Thyroxine treatment:*** The dose of levothyroxine will be higher than a normal replacement dose, as it is intended to suppress the level of serum TSH to undetectable. For example if the TSH is in the normal range the dose of levothyroxine will usually be ***increased***. Suppressive levothyroxine therapy is best supervised by a member of the thyroid cancer MDT. The GP will be advised of the target levels of TSH.
- ii. ***Treatment of hypocalcaemia:*** Patients taking calcitriol / alfacalcidol and /or calcium supplements must be monitored closely (for example every 3 months if generally stable, more frequently if not) to ensure that hypercalcaemia does not occur. The dose is kept to the minimum required to maintain serum calcium in the (low) normal range. Changes to the dose will usually be by 250 ng (0.25 µg).
- iii. The GP should ensure that the patient knows about and is offered:
 - ***MDT follow up*** – necessary for detection of early recurrence and complications and for their appropriate treatment.
 - Access to a member of the core team for support.

Appendix 1. Assay methodology

(i) MEASUREMENT OF THYROGLOBULIN

Many differentiated papillary and follicular carcinomas of the thyroid synthesise and secrete Tg. Detailed UK guidelines for measurements of relevant analytes have been published⁵⁵, and will be summarised here. Problems with Tg assays have been widely reviewed^{55,124,156,157,256,257}.

- i. There should be clear guidance from each laboratory to its users on specimen requirements and sample stability **(IV, C)**
- ii. The use of the Community Bureau of Reference standard for Tg (CRM 457) is recommended. **(IV, C).**
- iii. The use of a reference range derived from normal subjects is not recommended. The laboratory should ensure that users are aware that patients on levothyroxine suppressive therapy should ideally have an undetectable serum Tg⁵⁵ **(IV, C).**
- iv. Laboratories and manufacturers should determine and quote the minimum detection limit (MDL) of their assay based on functional sensitivity derived from patient samples. The MDL should ideally be $\leq 0.2\mu\text{g/L}$ **(IV, C).**
- v. Although a post-rhTSH serum Tg of $\geq 2\mu\text{g/L}$ has been suggested as a positive response justifying further investigations and treatment, this threshold may not be applicable for many of the currently available assays because of known differences in sensitivity, accuracy and precision **(IV, C).**
- vi. Laboratories and manufacturers should identify the analytical range of their Tg assay and adopt procedures to identify samples suffering from 'hook' effects **(IV, C).**
- vii. Laboratories and manufacturers should inform clinicians of the possibility of interference due to endogenous TgAb and indicate the most likely nature of the interference (false elevation/false reduction in measured Tg) **(IV, C).**
- viii. Identification of possible assay interference is best achieved using either TgAb measurements or discordance between Tg results obtained using immunometric assay and radioimmunoassay²⁵⁷. Recovery experiments alone are not recommended to identify assay interference²⁵⁶ **(IV, C).**
- ix. Tg autoantibodies should be measured in the same sample as serum Tg. The presence of Tg autoantibodies usually invalidates the serum Tg result but interference may also occur in the absence of Tg antibodies. If Tg autoantibodies are to be measured a sensitive immunoassay rather than a haemagglutination method should be used⁵⁵ **(IV, C).**
- x. For a particular Tg method it is highly desirable that the results of a clinical assessment of the assay performance should be available. The clinical sensitivity and specificity (i.e. positive and negative predictive values) of the assays should be quoted **(IV, C).**
- xi. Laboratories should run internal quality control samples, which encompass the range of results reported by the laboratory. A sample with a Tg concentration close to the minimum detection limit (MDL) should also be run with each assay to ensure that the quoted MDL is being achieved **(IV, C).**
- xii. Laboratories should participate in an accredited External Quality Assessment scheme **(IV, C).**

- xiii. Requesting clinicians should contact the laboratory before the collection of blood for Tg/TSH from patients post radioiodine administration (**IV, C**). The handling and transport of such radioactive samples is covered by legislation and such samples may not be accepted by the laboratory.

(ii) MEASUREMENT OF CALCITONIN

The following recommendations apply to the measurement of calcitonin (**IV, C**):

Timing of specimen collection

- i. Ideally a fasting morning specimen should be obtained to enable optimal comparison with reference values. If this is not possible, specimens can be collected at any time of day.
- ii. Post-operative samples should be collected at least ten days after thyroidectomy and should also be fasting samples if possible ^{55,224} (**III, B**).
- iii. For provocative testing samples are usually collected 5 minutes prior to administration of calcium /pentagastrin and then at intervals of 2, 5 and 7-10 minutes after ²¹³. Indications for provocative testing are listed in 14.2 iv.

Type of specimen

- i. Serum or plasma requirements should be confirmed with laboratories and/or manufacturers' kit inserts. The effect of gel tubes should be known (**IV, C**).
- ii. Calcitonin results may be affected by visible haemolysis or lipaemia and assay of such specimens should be avoided if possible

Specimen stability

Calcitonin in serum or plasma is unstable and blood specimens should be kept on ice. Red cells should then be separated within 30 minutes of collection and serum or plasma frozen immediately (**IV, C**).

Effects of other conditions, treatment and medication

- i. Previous treatment with monoclonal antibodies should be noted because of the potential for interference with human anti-mouse antibodies in immunometric assays (**IV, C**).
- ii. Chronic renal failure may increase basal calcitonin levels.
- iii. Mildly increased calcitonin may be observed in pregnancy, pernicious anemia, autoimmune thyroid disease, hypergastrinaemia and during the neonatal period.

Methodology

- i. Assays should be standardised using WHO International Standard IS 89/620 (**IV, C**).
- ii. Laboratories must decide whether to use a method that recognises primarily monomeric calcitonin (immunometric) or a method with broader specificity (RIA) (**IV, C**).

Assay sensitivity

Laboratories and/or manufacturers should determine and quote the minimum detection limit of their assay based on precision profiles derived from patient samples **(IV, C)**.

Assay interferences

Laboratories should have established protocols for identifying specimens that may have ‘hooked’ and specimens that may contain interfering antibodies **(IV, C)**.

Clinical assessment

For a particular calcitonin method the results of a clinical assessment of the assay performance should be available. The clinical sensitivity and specificity (i.e. positive and negative predictive values) of the assays should be quoted.

Quality assurance

- i. Laboratories should run internal quality control at concentrations appropriate for the range of results obtained. A pool with a calcitonin concentration close to the minimum detectable limit should also be run to ensure good baseline security **(IV, C)**.
- ii. Laboratories should participate in a recognised and accredited external quality assessment scheme **(IV, C)**.

Appendix 2, Recognition of MEN2B

MEN2B Clinical Features (*Reproduced with the consent of the patients*)

Please insert here the *.pdf file: 'MEN2B&W'

Appendix 3. Search methodology

Literature searches were carried out on a number of databases and world-wide web resources. Since there are few systematic reviews and randomised controlled trials in this area, a search strategy was designed to retrieve reviews and papers reporting on all primary studies including cohort studies, case control studies and other clinical trials. No limit was placed on language or age of subjects, and there were no limits placed on date of publication.

It was also necessary to limit searches to differentiated thyroid cancer, and exclude undifferentiated anaplastic thyroid cancer. The search therefore included the following items:

- Differentiated thyroid cancer
- Thyroid neoplasm
- Thyroid nodule
- Carcinoma- papillary, follicular
- Hürthle cell
- Medullary thyroid cancer
- Multiple endocrine neoplasia type 2

A medline search covered 1966-2006.

This was supplemented by searches on the Cochrane Library and a number of world-wide web resources, including:

- Cancerlit
- CancerNet
- National Guideline Clearinghouse
- National Research Register
- SIGN

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Appendix 5. Patient information

Patient representatives have been fully involved in each stage of development of the guidelines and the patient information literature.

1 Patient support groups

BACUP

3 Bath Place
Rivington Street
London
EC2A 3JR

British Thyroid Foundation

PO Box 97
Clifford
Wetherby
West Yorkshire
LS23 6XD

Butterfly North East

PO Box 205
Rowlands Gill
Tyne & Wear
NE39 2WX
Tel: 01207 545469
butterflynortheast@btopenworld.com

Association for Multiple Endocrine Neoplasia Disorders

AMEND (MEN2/FMTC)
31 Pennington Place
Southborough
Kent
TN4 0AQ
email: jo.grey@amend.org.uk

2 Web sites with useful information for patients

British Thyroid Foundation

<http://www.btf-thyroid.org>

AMEND (information re MEN syndromes)

<http://www.amend.org.uk>

Bacup

<http://www.cancerbacup.org.uk/> cancerBacup

Butterfly Northeast

<http://www.butterfly.org.uk>

Thyroid Foundation of America

<http://www.tsh.org/>

Cancernet

<http://www.thyroid-cancer.net/>

Endocrine Society information for patients

<http://216.205.53.178/endo/pubrelations/patientInfo/thyroid.htm>

Medline (search the medical literature)

<http://www.medlineplus.gov/>

Medline (information for patients)

<http://www.nlm.nih.gov/medlineplus/ency/article/001213.htm>

Thyroid Cancer Survivors' Association

<http://www.thyca.org/>

Patient Information Leaflet 1

The Thyroid Gland And Thyroid Cancer

Your Tests and Treatment

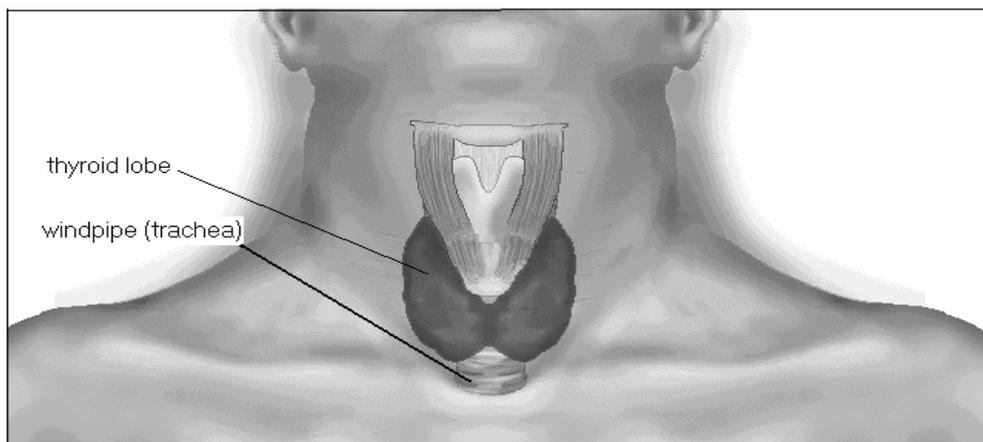
The thyroid gland

What is the thyroid gland?

The thyroid gland is an endocrine gland; this means that it makes hormones which are released into the bloodstream. Hormones act as messengers to affect cells and tissues in other parts of the body.

Where is the thyroid gland?

The thyroid gland is made up of two lobes (each about the size of half a plum) which are joined together by a ridge of thyroid tissue called the isthmus. The two lobes lie on either side of your windpipe, with the gland as a whole lying just below your Adam's Apple.



What does the thyroid gland do?

- The thyroid gland produces three hormones which it secretes into the bloodstream. The first is called 'Thyroxine' which contains four atoms of iodine and is often called T4. If little or no thyroxine is produced it can easily be replaced with medication.
- The second is called 'Triiodothyronine' which contains three atoms of iodine and is often called T3. In the cells and tissues of the body the T4 is converted into T3, and it is the T3 (derived from T4, or secreted as T3 from the thyroid gland) that is active and influences the activity of all the cells and tissues of the body. If little or no T3 is produced it can easily be replaced with medication.
- The third is called 'Calcitonin' which is produced in response to increased levels of calcium in the blood. Calcitonin helps to lower calcium and phosphate levels in the blood by promoting their excretion. This hormone is produced in excess when medullary thyroid cancer is present. If little or no calcitonin is produced the body can function perfectly well without it having to be replaced.

What do the thyroid hormones do?

Thyroid hormones affect the metabolism of your body cells; that is, they regulate the speed at which your body cells work. If too much of the thyroid hormones are secreted, the body cells work faster than normal, and you have 'hyperthyroidism'. However if too little of the thyroid hormones are secreted then the body cells work slower than normal, and you have 'hypothyroidism'.

How is the thyroid gland controlled?

Most glands work in conjunction with other glands, and the thyroid gland works with the pituitary gland. The thyroid is controlled by the pituitary, which lies underneath your brain in your skull and senses the levels of thyroid hormones in your bloodstream. If the levels drop below normal, the pituitary reacts by secreting a hormone called the 'thyroid stimulating hormone' which is often called TSH. TSH stimulates the thyroid gland to secrete more T3 and T4. Should the thyroid hormone levels rise above normal levels the pituitary senses this and stops secreting TSH and so the thyroid gland slows down its secretion of T3 and T4. If you need thyroxine medication this does not cause any problems to TSH.

How is thyroid activity measured?

Your doctor will be able to get a good assessment of your thyroid gland activity by taking a history of your symptoms and by a physical examination. However, to gain an exact level of the thyroid hormones, it is necessary to take a small sample of blood, which when analysed in the laboratory will show how much T4 and T3 is being secreted, and how active your pituitary is, by measuring the level of TSH. These tests are sometimes called thyroid function tests or TFTs.

What are the parathyroid glands and how do they affect calcium levels?

Another set of glands, that lie next to the thyroid gland, are the parathyroid glands. There are normally four parathyroids, although this can sometimes vary. The parathyroids produce Parathyroid Hormone (PTH) and this regulates the concentration of calcium in the blood. Normal calcium levels in the blood are essential for healthy bones, blood clotting, cardiac rhythm and function of the cells, as well as for general well-being.

Thyroid cancer

Most cancers of the thyroid gland are very slow growing and it may be many years before the symptoms present themselves.

Are all thyroid cancer the same?

No, there are different types:-

- **Papillary cell carcinoma** - This is the most common thyroid cancer. It is more common in younger people, particularly women.
- **Follicular cell carcinoma** - This is less common, and tends to occur in slightly older people than those with papillary cancer.
- **Medullary cell carcinoma** - This is a rare cancer, which is sometimes hereditary. Ask your specialist about genetic counselling and he/she will arrange it.

Most thyroid cancers are very treatable and curable, but there is the possibility of recurrence, specially in the very young and very old. This can occur at any stage, but recurrences **can** be treated successfully, so lifelong follow-up is most important.

What is the Cause of Thyroid Cancer?

The cause of thyroid cancer is unknown, however, a recognised risk factor is radiation exposure and it has been found in people who have had external radiotherapy to the neck 10 or 20 years previously as well as in “Chernobyl children”. Research into the causes of thyroid cancer is ongoing. Very occasionally papillary cancer is hereditary, and medullary cancer is quite often hereditary.

What are the Symptoms of Thyroid Cancer?

- A painless lump in the neck which gradually increases in size.
- Difficulty in swallowing (dysphagia) – because of pressure of the thyroid gland on the oesophagus (gullet).
- Difficulty in breathing (dyspnoea) - because of pressure of the thyroid gland and the trachea (windpipe).
- Hoarseness of the voice.
- Often there are no symptoms and it is found “by chance”.
- Symptoms of hyperthyroidism (overactive thyroid) and hypothyroidism (under active thyroid) are rare, as cancer cells do not generally affect hormone production from the thyroid.

What tests will I need?

Your GP will do a blood test to see if the thyroid hormone levels are within normal limits. While this does not in itself diagnose a cancer it does help your GP decide which specialist you will need to see next. Following your visit to your GP with one of the above symptoms, you will need to have some special investigations to confirm the diagnosis. These will be done in a specialist hospital clinic.

Fine needle aspiration - This is done in the out-patient hospital clinic. A sample of cells is extracted by means of a very small needle passed into any swelling you may have in your neck. These cells are then analysed under a microscope. This will be one of the main tests that will help confirm your diagnosis.

Blood test- Some additional blood tests may be done to recheck the function of your thyroid and levels of thyroid antibodies.

Ultrasound scan - In this test a picture of the thyroid gland is obtained by use of sound waves to show any solid lumps or cysts. Again this in itself cannot confirm cancer but it can help with the overall diagnosis and in planning treatment.

Radioisotope scan – This type of scan is occasionally helpful in assessing thyroid lumps. A tiny dose of radioactive iodine is given as a capsule (or alternatively another radioactive substance called “technetium” is given as an injection), then after a short time a gamma camera is placed over the neck. The camera measures the amount of radioactive substance taken up by the thyroid gland. Cancer cells do not absorb radioactive substances as well as normal thyroid cells, so a small cancer may show on the scan as a 'cold' nodule. However it is not a very good diagnostic test, and many so-called 'cold' nodules are benign.

What Treatment will I be offered?

You may be offered Surgery (thyroidectomy)

Surgery is usually the first line of treatment for thyroid cancer. Usually the whole thyroid gland (total thyroidectomy) will need to be removed, though sometimes it will be adequate to remove only one lobe; it depends on various factors such as your age, size of the lump and results of the tests mentioned above. The parathyroid glands may or may not be removed. After a thyroidectomy, thyroxine tablets will need to be taken as prescribed for the rest of your life; regular blood tests will be needed to check that the thyroid hormone levels are within normal limits, and that the TSH level is suppressed. Eventually you should only need a blood test once or twice a year.

Following surgery you will need to have your hormone levels monitored

Following your thyroid surgery you will be monitored by your General Practitioner (GP) regarding your thyroid medication and check up blood tests will be done. When you go home please contact your GP or treatment centre if you feel extremely tired, or have feelings of pins and needles in hands/feet/face, or if you have palpitations, feel shaky or become very over-active, or generally feel very unwell. This may mean you need to have your thyroxine or calcium levels checked and your medication dose increased, or decreased as the case may be. Once your body has settled you will be able to lead a normal life but you will need to continue to take the thyroxine tablets for the rest of your life and to have your thyroid tests checked regularly. It will be especially important to have your thyroid tests (TSH) checked if you become pregnant, as you may need to increase your dose of thyroxine (levothyroxine).

You will probably also need to have radioactive iodine treatment

Most people need to have radioactive iodine treatment following surgery. Your doctor will tell you if this is the case. Radioactive iodine treatment is painless, taken either as one or two capsule-type tablets, or as a liquid, in a single dose. You should not feel sick or lose any hair or have any other side effects with the usual dose required. It is a safe dose of radiation but for the safety of others for the first two to four days a person needs to reduce their social contact and to come into hospital. If you need this treatment you will be informed by your specialist consultant and given an information booklet before you start treatment.

Most thyroid cancers are very treatable and curable

Please contact your Specialist Treatment Centre Staff or your General Practitioner if you have any questions or concerns after reading this information book. Together we can help you through your investigations, information, treatment and recovery.

Useful Contacts

The British Thyroid Foundation

PO Box 97 Clifford, Wetherby, West Yorkshire LS23 6XD Tel no: 01423 709707/01423 709448

<http://www.btf-thyroid.org/>

Butterfly Northeast

PO Box 205, Rowlands Gill, Tyne & Wear NE39 2WX Tel: 01207 545469

www.butterfly.org.uk

Association for Multiple Endocrine Neoplasia Disorders AMEND (MEN2/FMTC)

31 Pennington Place, Southborough, Kent TN4 0AQ

<http://www.amend.org.uk>

email: jo.grey@amend.org.uk

Cancer BACUP

3 Bath Place, Rivington Street, bLondon, EC2A 3JR Tel no: 0800 800 1234

www.cancerbacup.org.uk

Macmillan Cancer Support

89 Albert Embankment, London SE1 7UQ Freephone 0808 808 2020

<http://www.macmillan.org.uk/home.aspx>

Cancerlink

Freephone Information Helpline 0800 132905

<http://www.personal.u-net.com/~njh/cancer.html>

CancerHelp UK

<http://www.cancerhelp.org.uk/>

Thyroid Cancer Survivors' Association

<http://www.thyca.org/>

Other useful sites can be found in the **BTA links page**

<http://www.btf-thyroid.org/>

Patient Information Leaflet 2

Thyroid surgery

Your thyroidectomy

What is a thyroidectomy?

A thyroidectomy is the removal of all (total thyroidectomy) or part of the thyroid gland (called “hemithyroidectomy” or “lobectomy”). You may need to have this done because you have a swelling or enlarged gland or for thyroid cancer treatment. Your specialist will explain to you whether a part or all of your thyroid needs to be removed, in order for you to give fully informed consent. If you do not understand any of the information please ask, as it is very important for you to make the right decision.

Is it a safe operation and what are the side-effects?

- The total removal of the thyroid gland means that you will need to take replacement hormone tablets called thyroxine every day for the rest of your life, otherwise you will experience symptoms of hypothyroidism (under active thyroid). Thyroxine tablets are the size of a sugar sweetener and safe to take. With monitoring by your specialist centre and or your general practitioner (GP) you should be able to lead an active and normal life.
- Thyroxine tablets are also given to suppress the level of TSH, and this is an important part of the treatment for thyroid cancer. So most patients will be given thyroxine even if they have only had part of the thyroid removed. You will be advised on this before you go home from hospital.
- You will need regular blood tests to measure the levels of hormones in your blood, and your medication will be adjusted accordingly. You will be given appointments for this.
- Thyroidectomy does not affect your ability to have children, but do ask your specialist for advice and information first if you are thinking of starting a family.

Will it affect my voice?

The thyroid gland lies close to the voice box (larynx) and the nerves to the voice box. Following your surgery you may find that your voice may sound hoarse and weak and your singing voice may be slightly altered, but this generally recovers quite quickly. In a very small number of cases this can be permanent.

Will my calcium levels be affected following thyroid surgery?

The parathyroids control the levels of calcium in the blood and are found close to the thyroid. Sometimes these glands are affected during surgery and if that is the case you may experience tingling sensations in your hands, fingers, in your lips or around your nose. Sometimes people may feel quite unwell. Please report this to the staff looking after you or, if at home, to your GP. Blood tests will be taken to monitor the levels of calcium in your blood following surgery. If the level of calcium is falling this can easily be treated by giving you calcium supplements, which may be given via an intravenous drip and/or by tablets. You may only need to take these tablets temporarily, as the parathyroids usually

resume normal function following removal of the thyroid. You will be advised by the medical and nursing staff.

Will I have neck stiffness, restricted shoulder movement or pain?

You will feel some discomfort and stiffness around your neck but you will be given some medication to help ease any pain and discomfort. Pain relief may be given in different ways, such as injections, liquid medicine or tablets. Most patients say the discomfort is not as bad as they expected and after the first day are up and walking around. After the first day following your surgery you will be given some gentle neck exercises to do; this may be given in an information sheet but please do ask staff if you are unsure. After a few weeks you should be back to a good standard of neck movement and shoulder function.

Will I have a scar?

Following your surgery, whether all or part of your thyroid is removed, you will have a scar, but once this is healed it is usually not very noticeable. The scar runs in the same direction as the natural lines of the skin on your neck

When will the operation be done?

You will probably have attended the out-patient clinic and may have been given a date for your operation at that time. Otherwise you may receive a date through the post or by phone from your Consultant's secretary.

What happens in a pre-admission assessment clinic?

- Some hospitals (not all) run a pre-admission assessment clinic, and you may be invited to attend one or two weeks before your operation. This enables both the doctors and the nurses to assess your health needs and carry out routine tests which may be required prior to surgery i.e. blood tests, a heart tracing (ECG) and a chest X-ray.
- The pre-admission assessment gives you the opportunity to meet the ward staff and to see where you will be admitted on the day of your operation. It is also a time when you can ask questions and discuss any concerns you may have about your operation and coming into hospital.
- Time is allocated for each individual and you should expect to be here no longer than 2 hours. However in exceptional circumstances a delay may be unavoidable.
- Some patients may have their investigations carried out the day before surgery and in that case would not be asked to attend the pre-admission assessment.

What about smoking?

All hospitals operate a No Smoking policy and smoking is not allowed on the ward. If you do smoke it is in your own health interests to stop smoking at least 24 hours prior to your anaesthetic.

Please contact your GP's surgery for advice on stopping smoking.

What shall I bring into hospital?

- Please bring nightwear, day wear, dressing gown, towels, toiletries, slippers, books/magazines and a pen. It will be helpful to arrange for a relative or friend to wash your nightwear etc and bring in fresh supplies. Hospital nightwear is available if required.
- **You must bring with you any medication you are currently taking, including inhalers.**
- Please do not bring any valuables with you, such as jewellery, large sums of money or bank cards. The hospital cannot take responsibility for your valuables. On your admission you will be asked to sign a disclaimer form which gives you the responsibility for any valuables you bring with you.
- Valuables may be taken for temporary safe keeping by the ward staff, while you have your operation and you will be issued with a receipt.

Will there be a bed?

- Because the Hospital runs an emergency service, it is not always possible to predict how many beds will be available. Also operations are carried out every day and clients are discharged home every day. It is therefore difficult to predict early in the morning how many beds will be available.
- You may be asked to take a seat in the waiting room until your bed is ready. You may be waiting for another person who has already had an operation to be discharged. The operation lists are planned and it is necessary to operate in a certain order due to many circumstances. It is for this reason that beds are allocated in order of operating lists and not in order of arrival. Please feel free to ask any member of staff for help and advice at any time. We will do our best to accommodate you and to keep you waiting for the least time possible.

What instructions or help will I have to get ready for surgery?

- Before your operation: when you have been taken to your bed the nurse will welcome you and check your details. It is necessary for you to wear a special theatre gown for your operation. This will be given to you by the nurse and she will show you how to wear it and give assistance if required.
- Please only wear cotton pants / underpants under your gown. All other underwear must be removed to ensure your safety during the use of the equipment in the operating theatre.
- You will also be given a pair of white elastic stockings to wear during and after the operation which will prevent blood clots forming in your legs. They feel quite tight and you may need help in putting them on.

What preparation will I need for the operation?

- Your operation will be carried out under a general anaesthetic which means that you are fully unconscious for the whole operation. Removing all or part of the thyroid involves delicate surgery which means that the operation can take about two hours.

- To prevent vomiting and other complications during your operation it is necessary that you should starve for at least 6 hours prior to your operation. You will be advised of what time you should starve from when you attend the pre-admission assessment or by letter from the Consultant's secretary.
- You should expect to be in hospital for about 4 days, or longer if any complications arise.
- If you would like to meet another patient who has had a thyroidectomy this can sometimes be arranged.

What will happen when I go to theatre?

- Just before going to theatre a checklist is completed by the nurse. You will then be taken on your bed to the operating theatre, usually by a theatre technician and a nurse. The nurse will stay with you in the anaesthetic room.
- Dentures, glasses and hearing aids can be taken out in the anaesthetic room and taken back to the ward by the nurse or you may like to put them in your locker before your operation.
- The anaesthetist will insert a small needle into the back of your hand through which you will be given the anaesthetic. The nurse will stay with you until you are fully under the anaesthetic and fully asleep. You will not wake up until the operation is over. You will be taken, on your bed, to the recovery area where a nurse will look after you until you are awake. You will then be taken back to the ward, on your bed, by a theatre technician and a nurse.

What will happen when I get back on the ward following surgery?

- Back on the ward you will be made comfortable. You will be sitting fairly upright in your bed supported by several pillows as this will help to reduce any neck swelling. Your nurse call bell will be situated close to you so that you can call a nurse at any time.
- You will have your blood pressure, pulse and oxygen levels checked frequently. A machine will do this automatically -- a blood pressure cuff is wrapped around your upper arm and a probe is clipped to one of your fingers.
- There will be a fluid drip going into a vein, probably in the back of your hand; this will be removed as soon as you are drinking normally (usually within 24 hours). You will be able to sip drinks quite soon after your operation as long as you are not feeling sick, and you can eat as soon as you feel you are able.

What will I look like after thyroid surgery and what will I be able to do?

- You will have a scar on the front part of your neck which will feel a little tight and swollen initially after the operation. It may feel a bit sensitive but should not cause any distress.
- You may have one or two wound drains from your wound to collect wound fluid which naturally occurs following your surgery. The drains are small plastic tubes which are inserted into the neck at the end of your operation. The long length of tubing outside the neck is attached to a plastic collection bottle into which the fluid drains. Wound drains help to speed up wound healing and reduce infection. The drains are not painful and you can carry them around with you. The drains will

be removed by a nurse and they are usually removed when the drainage is very minimal. The time span may vary but is usually a day or two after your operation.

- You will feel some discomfort and stiffness around your neck but you will be given some medication to help ease any pain and discomfort. Pain relief may be given in different ways such as injections, liquid medicine or tablets. Other patients say it is not as bad as they expected and after the first day are up and walking around.
- For your own safety it is important that you do not get out of bed on your own immediately following your operation as you may be drowsy and weak. At first when you need to use the toilet a member of staff will need to assist you with a commode or bedpan. You will soon be able to walk to the bathroom yourself.
- You will have a nurse call bell within easy reach so that you can seek help from the ward staff as needed.
- Following your operation you may not feel very sociable so it is wise to restrict visitors.

Will it affect my eating and drinking?

For a short period after your operation you may find it painful to swallow and you may need a softer diet for a short time. You may find that nutritious drinks are helpful in maintaining a balanced diet which is important to assist healing.

Will I have a sore neck?

You will probably find that your neck is quite sore and you will be given medication to take home to relieve the discomfort. Please take your medication as described on the packet and take care not to exceed the recommended number of tablets.

This medication should also ease the discomfort on swallowing. Your neck may appear swollen and hard to touch, with some numbness, which will gradually resolve as healing takes place.

What should I do to reduce any risk of wound infection?

Keep your neck wound clean and dry. Initially the nursing staff will check your wound daily and clean it as necessary. A few days following surgery when you are feeling more recovered you may have a shower or bath but take care to ask the nursing staff's advice first and gently pat the wound dry with a clean towel. Exposure to the air will assist wound healing.

If your neck becomes increasingly painful, red or swollen or you notice any discharge then please seek medical advice from ward staff or GP. To reduce the risk of infection it is wise to avoid crowded places and take extra care of yourself. Use only clean towels on your wound area for the first few weeks.

What care do I need to take regarding my neck wound?

Take care not to knock your wound and remember to keep it dry if it becomes wet after bathing or showering by patting it dry with a clean towel.

Once the scar has begun to heal, you can rub a small amount of unscented moisturising cream on the scar so it is less dry as it heals. Calendula, Aloe Vera or E45 cream (available from health shops) are effective. The pressure of rubbing the cream in will also help to soften the scar.

What rest do I need?

You will need to take it easy while your neck wound is healing. This means avoiding strenuous activity and heavy lifting for a couple of weeks. Your neck will gradually feel less stiff and you will soon be able to enjoy your normal activities.

What about my medications and tablets?

Please continue to take the medication you have been prescribed and ensure that you have a good supply. If you are unsure about any of the tablets you need to take please check this with a nurse before you go home. Repeat prescriptions can be obtained from your GP. When you come for your appointments at the hospital to check your blood levels following your thyroidectomy your medication may need to be altered so please check with the medical staff.

When should I return to work?

You will probably need to take 1-2 weeks off work (or sometimes longer) depending on your occupation and the nature of your work. The hospital can issue you with a note for 2 weeks and then you should see your GP if more time is required.

Will I need to be checked in an out-patient department following discharge home?

Following your discharge you will need to be reviewed in the out-patient clinic to check how your wound is settling down, your hormone levels and how you are feeling. You will usually receive the date and time for this appointment through the post or it may be given to you by the ward staff before you go home. Please contact the ward or the Consultant's secretary at the hospital if you do not receive one shortly following discharge. Depending on the problem with your thyroid and the results from the thyroid tissue that has been removed, you may be offered further treatment. This will be discussed with you by your specialist Consultant at your clinic appointment. If you would like any further information please do not hesitate to ask the nursing staff.

Will I be able to cope?

Most people when first told they need to have a thyroidectomy say they feel all sorts of mixed emotions, while others feel numb, some feel they knew all the time that they would need surgery. We are all individuals and cope in different ways and need different lengths of time to adjust to the changes we face.

You do not have to face your treatment on your own.

Support and help is available from the staff.

Together we can help you through your investigations treatment and recovery.

Useful Contacts

The British Thyroid Foundation

PO Box 97 Clifford, Wetherby, West Yorkshire LS23 6XD Tel no: 01423 709707/01423 709448
<http://www.btf-thyroid.org/>

Butterfly Northeast

PO Box 205, Rowlands Gill, Tyne & Wear NE39 2WX Tel: 01207 545469
www.butterfly.org.uk

Association for Multiple Endocrine Neoplasia Disorders AMEND (MEN2/FMTC)

31 Pennington Place, Southborough, Kent TN4 0AQ
<http://www.amend.org.uk>
email: jo.grey@amend.org.uk

Cancer BACUP

3 Bath Place, Rivington Street, bLondon, EC2A 3JR Tel no: 0800 800 1234
www.cancerbacup.org.uk

Macmillan Cancer Support

89 Albert Embankment, London SE1 7UQ Freephone 0808 808 2020
<http://www.macmillan.org.uk/home.aspx>

Cancerlink

Freephone Information Helpline 0800 132905
<http://www.personal.u-net.com/~njh/cancer.html>

CancerHelp UK

<http://www.cancerhelp.org.uk/>

Thyroid Cancer Survivors' Association

<http://www.thyca.org/>

Other useful sites can be found in the **BTA links page**

<http://www.btf-thyroid.org/>

Patient Information Leaflet 3

Radioactive iodine ablation and therapy

Things you need to know

Radioactive iodine “ablation” is treatment with radioactive iodine, intended to kill off any remaining thyroid tissue in the neck after a thyroid operation. Radio active iodine “therapy” refers to treatment with radioactive iodine with the intention to kill off thyroid cancer cells in the neck or elsewhere in the body. Radioactive iodine therapy is given only if the tests show that there is persistent tumour in the body. Most of what follows applies to both “ablation” and “therapy” and will be referred to as “radioactive iodine treatment”.

This form of treatment (ablation or therapy) consists of swallowing radioactive iodine either as a capsule or a liquid. The radioactive iodine is taken up by the thyroid gland. The very small dose of radiation is then concentrated in the thyroid cells and destroys them.

Is radioactive iodine treatment (ablation or therapy) safe?

Radioactive iodine has been used to treat thyroid cancer for over 50 years. The greatest danger from radioactive iodine is to the thyroid gland, but as your thyroid has been removed, it is not at risk; the treatment is meant to destroy any thyroid cells that may have escaped surgical removal. Radioactive iodine treatment has been linked with an increased risk of developing other cancers. In absolute terms, this risk is small, and has to be balanced against the benefits in treating the thyroid cancer. Your consultant will discuss these issues with you in detail before the treatment.

The precautions which are described below are intended to protect other people, and particularly pregnant women and young children. It makes sense to reduce everyone’s exposure to radioactivity, as any one of us may need this form of treatment in the future.

Are there any side effects from radioactive iodine treatment?

Most patients do not have side effects form radioiodine treatment. Some patients may experience a feeling of tightness in the throat and/or feel flushed, which usually lasts for no more than 24 hours. If this persists please inform the nursing staff. An anti-inflammatory drug can be given to relieve this problem. Some patients may lose their taste slightly. This can happen a few weeks after the treatment and should only last a few days. Drinking plenty of water after the treatment helps to wash out the radioactivity and reduces this problem. Please do talk through any of your questions with the specialist consultant or a member of the treatment team.

What if I am pregnant or feeding?

It is very important that you do not have radioactive iodine treatment if you are pregnant, or think there is a good chance that you may be. Please let your medical staff know if you are unsure before you have any treatment. It is important not to become pregnant when having investigations for thyroid cancer. You should use a reliable contraceptive for at least 6 months after radioactive iodine treatment. Long term, your fertility will not be affected even after repeated doses of radioactive iodine.

If you are breast feeding, you should stop this at least 4 weeks and preferably 8 weeks before you have the radioiodine treatment and not be restarted.

(Male patients) Will it affect my ability to have children?

Male patients are advised not to try for children (get their partners pregnant) for 4 months following radioactive iodine treatment and until they are sure they will not need any further radioactive iodine treatment. Long term your fertility should not be affected but there may be a small risk if repeated radioactive iodine therapy is needed. Please discuss this with your specialist consultant or a member of the treatment team before trying for a family following this treatment: specialist advice and help is available.

Before having radioactive iodine treatment what medication/tablets should I take?

If you are taking T3 tablets, most specialist centres recommend these should be stopped for 2 weeks before your radioactive iodine treatment.

If you are on levothyroxine tablets most specialist centres will advise you to stop taking them for 4 weeks before the radioactive iodine treatment. In this 4 week period your specialist may first change you to T3 tablets for 2 weeks, and then stop your tablets altogether for the last 2 weeks before your treatment. You may feel weak and tired when you are not taking your tablets. This is normal and will disappear once you start taking them again, usually a few days after you have had your radioiodine.

It is important that you follow the instructions regarding stopping your thyroxine medication given to you by your specialist centre staff, as it may vary in different centres. Please contact your specialist centre if you are unsure about your thyroxine medication, one month before your planned date for radioactive iodine treatment.

Should I keep taking my other medication/tablets?

If you are taking any other tablets you should carry on doing so and bring a supply with you on admission and show them to the doctor and nurse team. If you are taking any vitamin or mineral supplements or cod liver oil stop taking them around three weeks before your therapy to help reduce your iodine levels.

Before my Radioactive Iodine Therapy what should I eat?

A diet which is rich in iodine can reduce the effectiveness of the treatment. Therefore two weeks before coming in to hospital we recommend the following:

- **Do eat** fresh meat, vegetables, fresh fruit, pasta and rice. These are low in iodine.
- **Do not eat** glace and maraschino cherries which contain the colouring material E127. Food coloured by spices is allowed.
- **Do not take** cough medicine, iodised table salt, or sea salt as these contain iodine. Ordinary table salt is allowed.
- **Try to cut down on** dairy produce such as eggs, cheese, milk and milk products, as they all contain some iodine.

- **Avoid** fish, kelp and all seafood.
- **Avoid** vitamin supplements which contain iodine.

Do I have to come into hospital for radioactive iodine treatment?

Yes, you will probably need to stay in hospital for 3-6 days. How soon you go home depends on how quickly the radioactivity leaves your body.

What happens on admission?

On the ward you will be greeted and your details will be registered. You will then be issued with a hospital name band to wear, with your hospital registration number and a few details on it. One of the nursing staff will take your blood pressure, pulse and temperature as a routine procedure.

You will be given an explanation of the treatment and details about the room you will be staying in.

You will have the opportunity to ask any questions that you might have.

Your doctor will then come to examine you and check that you have stopped taking your thyroid tablets prior to the treatment, as this interferes with the absorption of the radioactive iodine. You will have been sent information regarding this with your appointment letter.

You will be asked to sign a form giving consent for the treatment.

Who gives the Capsule?

The Nuclear Medicine (or Medical Physics) department within the hospital is responsible for dealing with the radioiodine treatment. One of their staff will come to the ward to give you the capsule (which is about the size of an antibiotic capsule), or the liquid (which is colourless and tasteless).

What happens next?

For the first two hours after taking the capsule you should refrain from eating and drinking, to allow time for the iodine to be absorbed. After this time you should eat as normal and drink as much as possible and so that you pass urine frequently. This will flush the excess radioactive iodine out of your system.

Are there any restrictions?

As the treatment you have received is radioactive no young children or pregnant women are allowed to visit. Others may visit for a short time. Because you are *radioactive*, staff will spend only short periods of time in your room. When they bring in your meals and drinks they may stand behind a lead screen and you should try to remain on the opposite side of the room. Do not expect them to stay and chat for long periods of time but do not hesitate to contact them if you need anything.

What happens at mealtimes?

The nursing staff will bring you meals in your room. These meals may be served on paper plates and you may need to use plastic cutlery. When you have finished your meal these should be disposed of in a bin provided. If there is any unwanted food this needs to be sealed in a plastic bag and disposed of in the

bin. Alternatively, if ordinary plates and cutlery are used these will have to be washed up either in your room, or in a special kitchen. A waste disposal unit may be available to dispose of any unwanted food. Each day you will receive a menu to fill in for the next day. Drinks are provided in the morning, mid-morning, lunch time, tea time and night time. If you do not receive your meal for whatever reason please ring the nurses station, who will provide you with one. We will try our best to ensure this does not happen.

What self washing/hygiene should I do?

As you should be drinking a lot, you should also be using the toilet frequently. All your bodily fluids are radioactive so you must flush the toilet after use. If you spill or splash urine please contact the nursing staff.

Your sweat is also radioactive, so we advise you take a bath or shower daily. This may sound a little strange and alarming at first but please remember this is a safe dose of radiation and it is for your treatment and long term recovery.

Are there any other items I can bring in with me to help me relax or pass the time?

You may have brought DVDs, CDs, laptops, iPods, books, clothes and toiletries with you. These items may need to be monitored for contamination before they can be removed from your room. It may sometimes be necessary for us to keep some of your belongings if they are contaminated. They will be returned to you once they are no longer contaminated.

When can I go home?

The staff from Nuclear Medicine or Medical Physics will come to the ward to take measurements and they can then work out how much radiation is still in your body and if you are at a safe level to go home. You must stay in the iodine room until that time. Before going home you may have a whole body scan.

Will I still have any restrictions when I get home?

The Nuclear Medicine or Medical Physics staff will explain to you the restrictions you must observe when you go home, for example avoiding crowded places and limiting the people you come into contact with. They can work out exactly how many days you need to restrict yourself. The restrictions you are given may vary from other patients as some patients may be lower or higher in their radioactivity. You will be at an acceptable level to go home. These restrictions are to protect other people, specially pregnant women and children.

Medical or nursing staff will organise a new supply of thyroid tablets for you to take home and you will be told when to restart them .

Will I have to come back to the hospital?

You will need to be seen again in the outpatient department by your doctor. You will either be given an appointment when you leave the ward, or this may be sent to you later.

When everything is organised you are free to go home.

Will I need Radioactive Iodine treatment again?

The treatment may need to be repeated until all the remaining thyroid tissue has been destroyed. Some people require one ablation dose and some people require more than one treatment.

Please remember that this is a low dose of radiation and all these procedures are to protect you and others in case they should need to have radiation treatment in the future. The aim is to keep everybody's exposure to a minimum.

Please contact your specialist treatment centre staff if you have any questions or concerns after reading this Information book. Together we can help you through your investigations, treatment and recovery.

Useful Contacts

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