CLINICAL ENDOCRINOLOGY

VOLUME 81 SUPPLEMENT 1 JULY 2014

THE CLINICAL JOURNAL OF THE SOCIETY FOR ENDOCRINOLOGY AND THE ENDOCRINE SOCIETY OF AUSTRALIA

British Thyroid Association Guidelines for the Management of Thyroid Cancer

WILEY Blackwell

Guidelines for the management of thyroid cancer

Third edition

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British Thyroid Association

July 2014

Acknowledgements

Grateful thanks are expressed to the many reviewers of these guidelines. These included leading international experts in thyroid cancer, hospital specialists, and general practitioners. They devoted much time and care to considering the document and their recommendations and suggestions for improvements were most valuable. Special thanks to Dr Cathy Sturgeon for her contribution on calcitonin, Dr Alan Dodd for his contribution in grading some of the evidence and the patient leaders who worked on the patient information leaflets: Judith Taylor (British Thyroid Foundation), Kate Farnell (Butterfly Thyroid Cancer Trust), Liz Glenister (Hypopara UK), Jo Grey (Association for Multiple Endocrine Neoplasia Disorders – AMEND), Janis Hickey (British Thyroid Foundation) and Helen Hobrough (Thyroid Cancer Support Group – Wales). The authors also wish to thank Joanne Mullen, Librarian Newcastle upon Tyne Hospitals NHS Foundation Trust and Bernadette Coles, Cancer Research Wales Library, for performing the literature searches.

Mission statement

The British Thyroid Association is a non-profit making Learned Society of professional clinical specialist doctors and scientists in the United Kingdom who manage patients with thyroid disease and/or are researching into the thyroid and its diseases in humans.

Contents

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British Association of Head and Neck Oncologists
British Association of Otolaryngologists/Head and Neck Surgeons of ENT UK
British Association for Cytopathology
British Association of Surgical Oncology
British Nuclear Medicine Society
British Thyroid Association
British Society of Head and Neck Imaging
Joint Specialty Committee (Nuclear Medicine) of Royal College of Physicians
National Cancer Research Institute-Thyroid Cancer Subgroup
Royal College of Pathologists
Royal College of Physicians (Diabetes and Endocrinology Committee)
The Royal College of Radiologists
Royal College of Surgeons of England
Society for Endocrinology
Thyroid Cancer Forum-UK
UK Endocrine Pathology Society

Patient-led Organisations represented

Association for Multiple Endocrine Neoplasia Disorders
British Thyroid Foundation
Butterfly Thyroid Cancer Trust
Hypopara UK
Thyroid Cancer Support Group Wales

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Endorsements by professional organisations

These guidelines have been formally endorsed by the organisations listed below:

Association of Clinical Biochemists
Association for Multiple Endocrine Neoplasia Disorders
British Association for Cytopathology
British Association of Endocrine and Thyroid Surgeons
British Association of Head and Neck Oncologists
British Thyroid Association
British Thyroid Foundation
Butterfly Thyroid Cancer Trust
ENT UK
Hypopara UK
National Cancer Research Institute Thyroid Cancer Subgroup
Royal College of Pathologists
Royal College of Physicians of London
Royal College of Surgeons of England
Society for Endocrinology
The Royal College of Radiologists
Thyroid Cancer Forum-UK
Thyroid Cancer Support Group – Wales
UK Endocrine Pathology Society

Notes on the development and use of the guidelines

Development of the guidelines

The first edition of *Guidelines for the management of thyroid cancer in adults* was published by the Royal College Physicians 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, the British Association of Head and Neck Oncologists, the British Nuclear Medicine Society, the Society for Endocrinology and the British Thyroid Foundation) and external refereeing.

These guidelines were updated in 2006/7 by a subgroup representing the majority of the same professional organisations in the light of advances in diagnosis and management of thyroid cancer. They placed 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.

The group producing the 3rd edition of the guidelines includes several new contributors from a wider range of disciplines. The new edition incorporates recent evidence and promotes further the survivorship agenda by emphasising the importance of quality of life and sparing patients with low risk of recurrence or mortality, unnecessary treatments. Patient engagement and participation in decision making is highlighted. The role of new and emerging treatments in advanced disease is also included. Ultrasound of the neck performed by an expert operator is invaluable in the investigation of suspected cases of thyroid cancer and a new chapter is devoted to describing how to best utilise this technique. Additional chapters include microcarcinoma, anaplastic thyroid cancer and survivorship.

The patient information leaflets have been revised and extended in close collaboration with patient-led support organisations. All leaflets were checked for readability using the software tool http://www.online-utility.org/english/readability_test_and_improve.jsp to calculate the Flesch Readability Score (FRS) and the Flesch-Kincaid Grade Level (FKGL). FRS scores ranged between 46.63 and 57.19. FKGL scores ranged between 9.19 and 11.44. The grade level can be converted to UK values using the table on http://learning.covcollege.ac.uk/content/Jorum/CEH_Jorum/page_41.htm.

The present document is based on a UK consensus of opinion. It does not address thyroid lymphomas or metastases to the thyroid.

The updated guidelines were reviewed by several members of the previous guidelines 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, with the addition of appropriate arrangements for use in the specific centres (measure 11-1C-103i, National Cancer Peer Review Programme) (http://www.mycancertreatment.nhs.uk/wp-content/themes/mct/uploads/2012/09/resources_measures_HeadNeck_April2013.pdf). 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 and the responsible clinician 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 in adult patients, although childhood thyroid cancer is included briefly in Chapter 15 and Chapter 17 on medullary thyroid cancer. Guidelines on thyroid cancer in children can be found elsewhere.

It is hoped that the document will provide guidance for general practitioners, general physicians, endocrinologists, surgeons, oncologists, nuclear medicine physicians, radiologists, pathologists, 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 audits.

Funding: Development of the updated guidelines was generously supported by the British Thyroid Association.

Declaration of conflict of interests: Dr Gerrard has received support from Genzyme for attendance at educational meetings and participation in advisory boards, Dr Perros have received support from Genzyme for attendance at educational meetings. Dr Moss has received support from Genzyme for attendance at educational meetings and participated in advisory boards for Genzyme and Astrazeneca. Professor Thakker has received honoraria / lecture fees from Novartis, Lilly and Ipsen. Mrs J Taylor has received support from Genzyme for attendance at educational meetings and participated in workshops organized by Bayer Healthcare.

Types of evidence and grading of recommendations

The definition of types of evidence and the grading of recommendations used in the guidelines follow that recommended by SIGN 50.4

Key to evidence statements and grades of recommendations

Levels of evidence

1 High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias

1 Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias

1 Meta-analyses, systematic reviews, or RCTs with a high risk of bias

2 High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2 Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2 Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3 Non-analytic studies, e.g. case reports, case series

4 Expert opinion

Grades of recommendation

A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Good practice points

Important practical points for which there is not, nor is there likely to be, any research evidence are shown in the guidelines as Good Practice Points, and are marked with a tick box ☑.

Abbreviations

AGES	Age at presentation, Grade of tumour, Extent, Size of primary tumour
AMES	Age at presentation, Metastases, Extent, Size of primary tumour
ARSAC	Administration of Radioactive Substances Advisory Committee (part of Health Protection Agency)
ATA	American Thyroid Association
ATC	Anaplastic thyroid cancer
BAETS	British Association of Endocrine and Thyroid Surgeons
BAO-HNS	British Association of Otolaryngologists, Head & Neck Surgeons
CCH	C-Cell hyperplasia
CEA	Carcinoembryonic antigen
CT	Computed tomography
DTC	Differentiated thyroid cancer*
EBRT	External beam radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
ETA	European Thyroid Association
FACS	Fluorescent activated cell sorter
FNMTC	Familial non-medullary thyroid cancer
FDG	Fluoro-deoxy-glucose
FKGL	Flesch-Kincaid Grade Level
FMTC	Familial medullary thyroid cancer
FNAB	Fine-needle aspiration biopsy
FNAC	Fine-needle aspiration cytology
FRAX	Fracture Risk Assessment Tool
FTC	Follicular thyroid cancer*
FT4	free thyroxine
FVPTC	follicular variant papillary thyroid cancer
GP	General practitioner
IJV	Internal jugular vein
LNM	Lymph node metastasis
IMRT	Intensity modulated radiotherapy
MACIS	Metastases, Age at presentation, Completeness of surgical resection, Invasion (extra-thyroidal), Size
MALT	Mucosa associated lymphoid tissue
MDL	Minimum detection level
MDT	Multidisciplinary team
MEN	Multiple endocrine neoplasia
MIBG	Metaiodobenzylguanidine
Micro PTC	micro-papillary thyroid carcinoma
MRI	Magnetic resonance imaging
MRND	Modified radical neck dissection
MTC	Medullary thyroid carcinoma*
PACS	Picture archiving and communications system
PCCND	Prophylactic central compartment neck dissection
PDC	Poorly differentiated carcinoma
PET	Positron emission tomography
PTC	Papillary thyroid cancer
PTH	Parathyroid hormone
pTNM	pathologically staged according to Tumour size, Node metastases and distant Metastases
rhTSH	Recombinant human TSH
RIA	Radioimmunoassay
RIS	Radiology Information System
RCT	Randomised controlled trial
RRA	Radioiodine remnant ablation
SAN	Spinal accessory nerve
SEER	Surveillance, Epidemiology, and End Results
SIGN	Scottish Intercollegiate Guidelines Network
SCM	Sternocleidomastoid muscle
SPECT	Single-photon emission computed tomography
SRE	skeletal-related events
sTg	stimulated thyroglobulin
T3	Triiodothyronine (liothyronine)
THW	Thyroid hormone withdrawal
TFT	Thyroid function test
Tg	Thyroglobulin
TgAb	Anti-thyroglobulin antibodies
TNM	Staged according to Tumour size, Node metastases and distant Metastases
TSG	Tumour-specific group
TSH	Thyroid-stimulating hormone
US	Ultrasound
VTE	Venous thromboembolism
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 oncocytic follicular (Hürthle) cell carcinoma).

Key recommendations

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

Access to a multidisciplinary thyroid cancer team

i. The management of differentiated thyroid cancer (DTC) (a highly curable disease) and of MTC should be the responsibility of a specialist multidisciplinary team (MDT), membership of which will normally be appointed by the regional cancer network **(4, D).**

ii. The timeframe for urgent referrals should comply with the Department of Health targets (Chapter 3) (4, D).

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 **(4, D).**

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 **(4, D).**

Patient focus

i. Patients should be offered full verbal and written information about their condition and their treatment (Appendix 4) **(4, D)**.

ii. Patients should have continuing access to a member of the MDT for guidance and support **(4, D).**

Prognostic factors, staging, risk stratification and management of uncertainty in differentiated thyroid cancer

i. The TNM classification (7th edition) (Table 2.1) is recommended **(4, D).**

ii. The ATA post-operative risk stratification for risk of recurrence shown in Table 2.2 is recommended **(4, C).**

iii. Allocation to one of three response groups after Dynamic Risk Stratification (Table 2.3) is recommended **(2-, C).**

iv. When the evidence for or against a treatment is inconclusive and no well designed, peer reviewed randomised or prospective national or institutional studies are ongoing to address this issue or if available, declined by the patient, these guidelines recommend a personalised approach to decision making **(Personalised Decision Making) (4, D).**

Presentation, diagnosis and referral

i. Patients should be referred to a surgeon, endocrinologist, or nuclear medicine physician who has a specialist interest in thyroid cancer and is a core member of the MDT **National Cancer Peer Review Programme, measure 11-1D-103i**

ii. US is an extremely sensitive examination for thyroid nodules. It can be specific for the diagnosis of thyroid carcinoma (particularly papillary carcinoma), and aids decision making about which nodules to perform FNAC. US also consistently increases the yield of diagnostic FNACs (Chapter 4). **Good Practice Point** ☑

iii. Undergoing investigations for a lump may be a stressful experience for the patient, which is exacerbated by inadequate or misleading information and by excessive waiting times for tests. High quality information about the individual's risk of having thyroid cancer and the complexities and limitations of diagnostic tests to exclude thyroid cancer should be provided to patients **(4, D).**

iv. The patient should be informed of the diagnosis of cancer by a member of the MDT in person, ideally in the presence of a nurse, during a private, uninterrupted consultation. Patients should be offered the opportunity to have a relative or friend present during the consultation **(4, D).**

Ultrasound assessment of thyroid nodules

i. The use of the U1-U5 scoring/grading system is recommended for assessing risk of malignancy and guiding FNAC **(2+, C).**

ii. US appearances that are indicative of a benign nodule (U1-2) should be regarded as reassuring not requiring fine needle aspiration cytology (FNAC), unless the patient has a statistically high risk of malignancy (Chapter 3.7) **(2++, B).**

iii. If the US appearances are equivocal, indeterminate or suspicious of malignancy (U3-5), an US guided FNAC should follow **(2++, B).**

iv. Nodules with Thy2 cytology but indeterminate or suspicious US features should undergo repeat FNAC for confirmation. The rate of malignancy in this setting is significant, and evidence supports repeat cytological sampling **(2++, B).**

v. Nodules detected by PET-CT with focal FDG activity should be investigated with ultrasound and FNAC, unless disseminated disease is identified and the prognosis from an alternative malignancy would preclude further investigation **(1++, A).**

Fine-needle aspiration cytology

i. Thyroid cytology should be reported by a cytopathologist with experience in such samples and with access to colleagues with additional experience for second opinions when appropriate. Such review increases accuracy of cytology **(2+, C).**

ii. The cytology report should contain a descriptive section interpreting the findings, followed by the Thy numerical category as defined by RCPath (section 5.2). **Good Practice Point** ☑

Surgery for differentiated thyroid cancer

i. The surgeon should have training and expertise in the management of thyroid cancer and be a core member of the multidisciplinary team (MDT) (Improving outcomes in Head and Neck Cancer http://www.nice.org.uk/nicemedia/live/10897/28851/28851.pdf)

ii. In patients with thyroid cancer assessment of extra-thyroidal extension and lymph node disease in the central and lateral neck compartments should be undertaken pre-operatively. A combination of ultrasound (US) and computed tomography (CT) / MRI imaging is advised depending upon local expertise. **Good Practice Point** ☑

iii. For patients with Thy3f or Thy4 FNAC a diagnostic hemithyroidectomy is recommended **(3, D).**

iv. Total thyroidectomy is recommended for patients with tumours greater than 4 cm in diameter, or tumours of any size in association with any of the following characteristics: multifocal disease, bilateral disease, extra-thyroidal spread (pT3 and pT4a), familial disease, and those with clinically or radiologically involved nodes and / or distant metastases **(2-, D).**

v. Central compartment neck dissection is not recommended for patients without clinical or radiological evidence of lymph node involvement, who have all of the following characteristics: classical type PTC, <45 years, unifocal tumour, ≤4 cm, no extra-thyroidal extension on US **(1-, C).**

vi. Patients with follicular cancer >4 cm tumours appear to have worse prognosis and should be treated with total thyroidectomy **(3, D).**

vii. Patients planned to receive radioiodine remnant ablation (RRA) with recombinant human TSH (rhTSH) after total/near-total thyroidectomy, should commence on suppressive doses levothyroxine (2 mcg per kg body weight). Lower doses should be considered in obese patients. If a thyroid hormone withdrawal protocol is followed, triiodothyronine (T3) (usual adult dosage 20 mcg tds) may be used and should be stopped for two weeks before RRA **(4, D).**

Management of papillary microcarcinoma

i. Thyroid lobectomy is recommended for patients with a unifocal microPTC and no other risk factors (Table 8.1) **(2+, C).**

Radioiodine remnant ablation and therapy for differentiated thyroid cancer

i. A clinical oncologist or nuclear medicine physician with expertise and an interest in the management of DTC should supervise this treatment and be a core member of the MDT **(4, D).**

ii. Patients in the "definite indications" category (tumour >4 cm, or any tumour size with gross extra-thyroidal extension (pT4), or distant metastases present) should be advised to receive RRA **(2+, C).**

iii. Patients in the "no indications" category (tumour ≤1 cm unifocal or multifocal, and on histology - classical papillary or follicular variant or follicular minimally invasive without angioinvasion and no invasion of thyroid capsule) should be advised against receiving RAA **(2+, C).**

iv. The patient should be seen by an appropriate member of the MDT (an Administration of Radioactive Substances Advisory Committee (ARSAC) Certificate holder), preferably in a multidisciplinary clinic, for assessment and discussion about the indication for RRA (or ^{131}I therapy). Informed consent should be obtained from the patient before treatment. **Good Practice Point** ☑

v. RRA and ^{131}I therapy must be administered by centres suitably equipped and certified for the purpose **Good Practice Point** ☑

vi. rhTSH is the recommended method of preparation for RRA in patients who have the following characteristics: pT1 to T3, pN0 or NX or N1, and M0 and R0 (no microscopic residual disease) **(1++, A).**

vii. Pregnancy must be excluded before RRA or ^{131}I therapy is administered in women of reproductive age (Chapter 14) **(3, D).**

viii. Breastfeeding must be discontinued at least 8 weeks before RRA or ^{131}I therapy to avoid breast irradiation and should not be resumed until after a subsequent pregnancy **(4, D).**

ix. If the patient undergoes THW, levothyroxine should be restarted when the patient is discharged following their ^{131}I treatment **(4, D).**

x. A post-ablation scan should be performed after ^{131}I when residual activity levels permit satisfactory imaging (usually 2-10 days) **(2++, B).**

xi. A stimulated Tg and neck US should be performed in preference to a diagnostic ^{131}I WBS between 9 and 12 months from RRA **(2+, C).**

xii. The principal indications for a diagnostic WBS after RRA, is in cases where measurement of serum Tg is unreliable, and where ^{131}I uptake was visualised beyond the thyroid bed and neck in the post-ablation scan **(4, D).**

xiii. Patients treated with total thyroidectomy and RRA and should undergo Dynamic Risk stratification **(3, D).**

External beam radiotherapy for differentiated thyroid cancer

i. The indications for consideration of adjuvant EBRT are for patients with a high risk of recurrence / progression with: (a) gross evidence of local tumour invasion at surgery with significant macroscopic residual disease, or (b) residual or recurrent tumour that fails to concentrate radioiodine i.e. loco-regional disease where further surgery or radioiodine is ineffective or impractical **(2-, D).**

Post-treatment follow-up of patients with differentiated thyroid cancer

i. Before committing patients with post-thyroidectomy hypocalcaemia to life-long substitution therapy with alfacalcidol / calcitriol and calcium, an attempt should be made to wean them off supplements in an outpatient setting **(4, D).**

ii. Patients on long-term alfacalcidol / calcitriol treatment should be monitored for adverse effects, which include hypercalcaemia, hypercalciuria, renal impairment, nephrocalcinosis and kidney stones. Thus, serum calcium tests should be undertaken at 3 monthly intervals or more frequently until the biochemistry is stable. Estimations of urinary calcium excretion, serum calcium and creatinine and ultrasonography (US) of the kidneys, should be performed annually. The occurrence of these adverse effects should necessitate a reduction (or cessation) of the dose of alfacalcidol / calcitriol **(4, D).**

iii. Following initial treatment with total thyroidectomy and radioiodine remnant ablation (RRA), and before evaluation of the patient's response to treatment after 9-12 months, TSH should be suppressed to below 0.1 mU/l in all patients **(4, D)**.

iv. For historical patients who have not undergone Dynamic Risk Stratification, it is recommended that serum TSH should be suppressed below 0.1 mU/l for 5-10 years. This suppression can then be relaxed as appropriate, based on clinical, radiological or biochemical assessment of response **(4, D).**

v. In specific at risk patient groups such as post-menopausal women, assessment of the 10-year probability of osteoporotic fragility fracture should also be performed using the WHO Fracture Risk Assessment Tool (FRAX (Table 11.1) **(4, D).**

vi. 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 measured **(4, D).**

vii. Samples should not be collected sooner than 6 weeks post-thyroidectomy or RRA / ^{131}I therapy **(2+, C).**

viii. rhTSH is the method of choice for thyroglobulin stimulation **(1+, B).**

Recurrent / persistent differentiated thyroid cancer

i. Surgery with curative intent is the treatment of choice for recurrent disease confined to the neck **(2+ C).**

ii. The choice of imaging should be guided in the first instance by the symptoms and clinical assessment of the patient, which may point to a particular anatomical area, bearing in mind that the commonest sites of recurrent disease are cervical / mediastinal lymph nodes, lungs and bones **(4, D).**

Long-term follow-up of differentiated thyroid cancer

i. Low-risk cases (for definition of low risk, see Chapter 2.3, Table 2.2) who have completed their treatment, are shown to be free of disease at five years and 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 primary care following agreement of well defined protocols and re-referral pathways **(4, D).**

Thyroid nodules and thyroid cancer in pregnancy

i. The pre-conception TSH goal in women with DTC, which is determined by risk stratification (Chapter 11.5), should be maintained during pregnancy. The dose of levothyroxine needs to be empirically increased as soon as pregnancy is confirmed, usually by approximately 30%, as requirements increase during pregnancy except in women receiving suppressive doses of levothyroxine **(2++, B).**

ii. Thyroid function should be evaluated as soon as pregnancy is confirmed. The adequacy of levothyroxine treatment should be monitored approximately every 4 weeks until 16-20 weeks of gestation and at least once per trimester thereafter. Serum TSH should be checked 4 weeks after each levothyroxine dose change **(3, D).**

iii. Breastfeeding must be discontinued at least 8 weeks before radioiodine remnant ablation (RRA) or ^{131}I therapy to avoid breast irradiation and should not be resumed, until after a future pregnancy (Chapter 9.2) **(4, D).**

Pathology reporting, grading and staging of thyroid cancers

i. Histopathologists reporting thyroid tumours should have a special interest in thyroid pathology or participate in a network with the opportunity of pathology review **(2+, C).**

ii. Cases should be handled and reported according to the current dataset of the Royal College of Pathologists (RCPath) 2014 **(4, D).**

iii. Pathological staging should be performed using the 7th edition of the TNM classification **(4, D).**

Medullary thyroid cancer

i. All patients with or, at risk of MTC should be referred for investigation / surgical treatment to a cancer centre **(4, D).**

ii. In all cases, a comprehensive family history must be taken to include first- and second- degree relatives to search for features of MTC or other endocrinopathies that may occur in individuals with familial MTC. This includes a history of unexpected sudden death, which should raise the suspicion of occult phaeochromocytoma **(4, D).**

iii. The initial evaluation of patients with suspected MTC includes US of the thyroid, FNAC and a baseline value for calcitonin, which may confirm the diagnosis and can indicate the likelihood of remission and extent of disease (Appendix 1.2) (**2+, C).**

iv. In all cases at least one 24-hour urine sample assayed for catecholamines and nor / metanephrines or plasma nor / metanephrines is required to exclude phaeochromocytoma, and a serum calcium to exclude hyperparathyroidism. These tests must be performed in all MTC patients prior to neck surgery even in the absence of a positive family history or symptoms **(4, D).**

v. In all confirmed cased of MTC, RET mutation analysis to establish the possible genetic basis for the disease within an individual or kindred, should be performed even in the absence of a positive family history. **Good Practice Point** ☑

vi. Patients with established MTC should undergo a minimum of total thyroidectomy and central compartment node dissection, the inferior limit of the dissection being the inominate artery (levels VI and VII) **(2+, C).**

vii. Prophylactic surgery should be offered to disease-free carriers of germ line RET mutations, identified by genetic screening. The possibility of future surgery should be discussed with parents before testing children. In ideal circumstances these individuals 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. This will depend upon the genotype and the age of the patient. Basal calcitonin levels indicate the likelihood of MTC ± node metastases. It is important to distinguish the need for therapeutic surgery from prophylactic surgery. **Good Practice Point** ☑

viii. Lifelong follow-up is recommended **(4, D).**

ix. If expertise is not available within the primary clinical team, the patient should be offered genetic counseling and referred to the clinical genetics service **(4, D).**

x. Patients with no special clinical features should be tested first for RET mutations in exons 10 and 11; if these are negative, for exons 13–16 (2-, D). Failure to screen exons 13–16 constitutes an incomplete test.

Anaplastic thyroid cancer

i. Initial assessment should focus in identifying the small proportion of patients with localised disease and good performance status, that may benefit from surgical resection and other adjuvant therapies **(4, D).**

ii. The surgical intent should be gross tumour resection and not merely an attempt at debulking. **Good Practice Point** ☑

Thyroid cancer: a guide for general practitioners

i. The GP should be informed of the diagnosis of thyroid cancer being communicated to the patient for the first time by the end of the following working day.

National Cancer Peer Review Programme, measure11-2I-111.

Research and audit

i. Patients should be informed about and given the opportunity to consider participation in ongoing randomized clinical trials in cases where there is genuine clinical equipoise or lack of level 1 evidence **(4, D).**

ii. Audit of various aspects of the service should be an ongoing process at network and national level. (http://www.mycancertreatment.nhs.uk/wpcontent/themes/mct/uploads/2012/09/resources_measures_HeadNeck_Measures_April2011.pdf).

National Cancer Peer Review Programme, measure 11-1C-111i

CHAPTER 1

1 Introduction

1.1. The need for guidelines

In spite of advances in diagnostic methods, surgical techniques and clinical care, there are differences in survival of patients with thyroid cancer in different countries, and the outcome in the UK prior to 1989 appeared to be worse than in other western European nations.[1] The reasons for this are unclear and may be multifactorial. There is a sense that outcomes in the UK are improving, but only long term national registry data can confirm or refute this in future. However, it may not be unreasonable to speculate that the impact of previous editions of these guidelines, and recent changes in cancer services within the National Health Service may have contributed. These include mandatory specialist multidisciplinary team management of all cancers (http://www.mycancertreatment.nhs.uk/wp-content/themes/mct/uploads/2012/09/resources_measures_HeadNeck_Measures_April2011.pdf), regular ma ndatory national peer review, equity of access to specialist care, the cancer drug fund, national cancer research groups supporting trials, patient support groups, national audits by professional organisations, the cancer reform strategy and survivorship programme. It is hoped that the third edition of the national guidelines for thyroid cancer, and their implementation through local protocols of the NHS networks, will continue to facilitate this process and improve care and outcomes in the UK.

1.2. Aim of the guidelines

The intention is to provide guidance for all those involved in the management of patients with differentiated thyroid cancer (DTC) and some of the rarer thyroid cancers. This document is not intended as guidelines for management of thyroid nodules, though the role of ultrasound (US) in assessing thyroid nodules is included. A summary of the key recommendations for the management of adult differentiated thyroid cancer, medullary thyroid cancer (MTC) and anaplastic thyroid cancer is provided (see previous section). Randomised trials are often not available in this setting. Therefore, evidence is based on large retrospective studies and the level of evidence is ascribed according to the Scottish Intercollegiate Guidelines Network 50 (A guideline developer's handbook (http://www.sign.ac.uk/pdf/sign50.pdf).

The three main aims of the guidelines are:

- to improve the referral pattern and management of patients with thyroid cancer;
- 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.

These guidelines do not address thyroid lymphomas or metastases to the thyroid.

1.3. Incidence

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 year.[2] In 2010, data from Cancer Research UK indicate 2654 new cases in the UK and 346 deaths. (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/thyroid/uk-thyroid-cancer-statistics). Annual incidence data for the UK from 2008 show 5.1 per 100 000 women and 1.9 per 100 000 men (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/thyroid/uk-thyroid-cancer-statistics). Thyroid cancer is the most common malignant endocrine tumour, but represents only about 1% of all malignancies.[2]

The incidence of thyroid cancer is increasing globally, mostly due to PTC,[3] including in the paediatric population.[4] The bulk of the increase is lower stage cancers and/or incidental micropapillary thyroid cancers found when surgery is performed for thyroid diseases other than cancer.[5,6] Overall mortality from thyroid cancer has remained stable over many years.[7] It has been suggested that the increase in incidence of thyroid cancer is due to better detection of incidental microcarcinomas.[7,8] This view has been challenged by studies which found that the incidence of thyroid cancers of all sizes has been increasing over time.[3,9] It seems plausible that factors other than increased detection, may underlie the rising incidence of thyroid cancer, and may include changing iodine status and exposure to radiation,[10] but in most cases the cause is unknown.

1.4. Public health and prevention

Nuclear fallout 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; exposure to these sources should be limited whenever possible. In cases of populations or individuals being contaminated with ^{131}I the thyroid can be protected by administering potassium iodide.[11–13]

1.5. Screening

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

familial MTCs 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*, *PPARG* and *p53*, have been identified. Testing for these genes is not routinely available in clinical practice.[14]

The following are considered to be risk factors for thyroid cancer[15–26]:

- 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;
- obesity.

i While screening generally is not indicated, 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 **(4, D).**

1.6. Research

In the past, randomised trials were very rare, and robust evidence for or against a treatment were not frequently available for early and advanced thyroid cancers. Although this is slowly improving, clinicians still have to deal with management of uncertainty or clinical equipoise frequently. In such cases participation in clinical trials in pursuit of level 1 evidence is important.

i Patients should be informed about and given the opportunity to consider participation in ongoing randomized clinical trials in cases where there is genuine clinical equipoise or lack of level 1 evidence **(4, D).**
Key recommendation

References

1 Teppo, L. & Hakulinen, T. (1998) Variation in survival of adult patients with thyroid cancer in Europe. *European Journal of Cancer*, **34**, 2248–2252.
2 Coleman, P.M., Babb, P., Damiecki, P. *et al.* (1999) Cancer Survival Trends in England and Wales 1971–1995: Deprivation and NHS Region. Series SMPS No. 61. Stationery Office, London, 471–478.
3 Sipos, J.A. & Mazzaferri, E.L. (2010) Thyroid cancer epidemiology and prognostic variables. *Clinical Oncology (Royal College of Radiologist)*, **22**, 395–404.
4 Hogan, A.R., Zhuge, Y., Perez, E.A. *et al.* (2009) Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. *Journal of Surgical Research*, **156**, 167–172.
5 Griniatsos, J., Tsigris, C., Kanakis, M. *et al.* (2009) Increased incidence of papillary thyroid cancer detection among thyroidectomies in Greece between 1991 and 2006. *Anticancer Research*, **29**, 5163–5169.
6 Hoang, J.K., Raduazo, P., Yousem, D.M. *et al.* (2012) What to do with incidental thyroid nodules on imaging? An approach for the radiologist. *Seminars in Ultrasound, CT and MR*, **33**, 150–157.
7 Davies, L. & Welch, H.G. (2006) Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA*, **295**, 2164–2167.
8 Harach, H.R., Franssila, K.O. & Wasenius, V.M. (1985) Occult papillary carcinoma of the thyroid: a "normal" finding in Finland: a systematic autopsy study. *Cancer*, **56**, 531–538.
9 Chen, A.Y., Jemal, A. & Ward, E.M. (2009) Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. *Cancer*, **115**, 3801–3807.
10 Wartofsky, L. (2010) Increasing world incidence of thyroid cancer: increased detection or higher radiation exposure? *Hormones*, **9**, 103–108.
11 Administration of Radioactive Substances Advisory Committee (2006) Notes for Guidance on the Clinical Administration of Radiopharmaceuticals and Use of Sealed Radioactive Sources. ARSAC, Didoct, Oxon. www.arsac.org.uk/notes_for_guidence/index.htm.
12 International Atomic Energy Agency (1991) Intervention Criteria in a Nuclear or Nuclear Radiation Emergency. Safety series number 109. IAEA, Vienna.
13 International Commission on Radiological Protection (1991) ICRP Publication 63: Principles for Intervention for Protection of the Public in Radiological Emergency. Pergamon Press, Oxford.
14 Giordano, T.J., Kuick, R., Thomas, D.G. *et al.* (2005) Molecular classification of papillary thyroid carcinoma: distinct BRAF, RAS, and RET/PTC mutation-specific gene expression profiles discovered by DNA microarray analysis. *Oncogene*, **24**, 6646–6656.
15 Schlumberger, M., De Vathaire, F., Travagli, J.P. *et al.* (1987) Differentiated thyroid carcinoma in childhood: long term follow-up of 72 patients. *Journal of Clinical Endocrinology and Metabolism*, **65**, 1088–1094.
16 Hancock, S.L., Cox, R.S. & McDougall, I.R. (1991) Thyroid disease after treatment of Hodgkin's disease. *New England Journal of Medicine*, **325**, 599–605.
17 Ron, E., Lubin, J.H., Shore, R.E. *et al.* (1995) Thyroid cancer after exposure of external radiation: a pooled analysis of seven studies. *Radiation Research*, **141**, 259–277.
18 Thompson, D.E., Mabuchi, K., Ron, E. *et al.* (1994) Cancer incidence in atomic bomb survivors. Part II: solid tumors, 1958–1987. *Radiation Research*, **137**(Suppl 2), S17–S67.
19 Winship, T. & Rosvoll, R.V. (1970) Thyroid carcinoma in childhood: final report on a 20 year study. *Clinical Proceedings – Children's Hospital of the District of Columbia*, **26**, 327–348.
20 Franceschi, S., Boyle, P., Maisonneuve, P. *et al.* (1993) The epidemiology of thyroid carcinoma. *Critical Reviews in Oncogenesis*, **4**, 25–52.
21 Levi, F., Franceschi, S., la Vecchia, C. *et al.* (1991) Prior thyroid disease and risk of thyroid cancer in Switzerland. *European Journal of Cancer*, **27**, 85–88.
22 Preston-Martin, S., Berenstein, L., Pike, M.C. *et al.* (1987) Thyroid cancer among young women related to prior thyroid disease and pregnancy history. *British Journal of Cancer*, **55**, 191–195.

23 Mack, W.J. & Preston-Martin, S. (1998) Epidemiology of thyroid cancer. In: J.A. Fagin ed. Thyroid cancer, Vol. 2. Kluwer Academic Publishers, Boston, 1–25.
24 Holm, L.E., Blomgren, H. & Lowhagen, T. (1985) Cancer risks in patients with chronic lymphocytic thyroiditis. *New England Journal of Medicine*, **312**, 601–604.
25 Kitahara, C.M., Platz, E.A., Freeman, L.E. *et al.* (2011) Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of five prospective studies. *Cancer Epidemiology, Biomarkers & Prevention*, **20**, 464–472.
26 Dal Maso, L., La Vecchia, C., Franceschi, S. *et al.* (2000) A pooled analysis of thyroid cancer studies. V. Anthropometric factors. *Cancer Causes and Control*, **11**, 137–144.

CHAPTER 2

2 Prognostic factors, staging, risk stratification and management of uncertainty in differentiated thyroid cancer

The long-term outcome of patients treated effectively for differentiated thyroid cancer (DTC) is usually favourable. The overall 10-year survival rate for middle-aged adults with DTC is 80–90%. However, 5–20% of patients develop local or regional recurrences and 10–15% distant metastases.[1–3] Nine per cent of patients with a diagnosis of thyroid cancer die of their disease.[4,5]

It is important to assess both risk of death from the disease and risk of recurrence 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.

2.1. Prognostic factors

Several factors have been shown consistently to be important for predicting death and recurrence in multivariate analyses of large patient cohorts:

Age. Age at the time of diagnosis is one of the most consistent prognostic factors in patients with DTC. The risk of recurrence and death increases with age, particularly after the age of 40 years.[6–11] Young children, under the age of 10 years, are at higher risk of recurrence than older children or adolescents.[12–15]

Gender. The male gender has been reported as an independent risk factor in some but not all studies.[4,9,10,14,15]

Histology. The prognosis of papillary thyroid carcinoma (PTC) is better than that of follicular thyroid cancer (FTC). However, if the confounding effects of age and extent of tumour at diagnosis are removed, survival rates are comparable.[6,9,17–19] Within the PTC group, poorer prognosis is associated with specific histological types (e.g. tall cell, columnar cell)[20–24] and the degree of cellular differentiation and vascular invasion.[7,25] 'Widely invasive' and 'vascular invasion' are features of follicular cancers associated with a poorer prognosis.[26] Poorly differentiated and oncocytic follicular (Hürthle-cell) carcinomas are also associated with a poorer outcome.[9,10,14,27–29]

Tumour extent. The risk of recurrence and mortality correlates with the size of the primary tumour.[6,8–11,16,27] Extra-thyroidal invasion,[6,8–11,25,30,31] lymph node metastases,[6,9,10,27,32] and distant metastases[25,33–35] are all important prognostic factors.[14]

2.2. Staging systems

Several staging systems have been proposed for DTC and continue to evolve.[36,37]

The most commonly used are:

- TNM **Tumour** size, **Node** metastases and distant **Metastases**
- AMES **Age** at presentation, **Metastases, Extent, Size** of primary tumour
- MACIS **Metastases, Age** at presentation, **Completeness** of surgical resection, **Invasion** (extra-thyroidal), **Size**
- EORTC European Organisation for Research and Treatment of Cancer methodology
- AGES **Age** at presentation, **Grade** of tumour, **Extent, Size** of primary tumour

Any of these systems can be used to assign patients to the high-risk or low-risk group (MACIS is used only for PTC), based on well-established prognostic factors (detailed below), but TNM and MACIS probably yield the most useful prognostic information.[38,39] The TNM classification is used extensively for registration and predicts mortality (Table 2.1) (for online calculator see: http://www.thyroid.org/thyroid-cancer-staging-calculator/).

2.3. Use of prognostic systems in DTC for stratified management

From the clinical standpoint, the objective is to tailor treatment to the individual so as to minimise the risk of death and recurrence. Equally important, is avoidance of unnecessary exposure of patients with a good prognosis to invasive therapies associated with long-term side effects, which may impact on quality of life. The principles of personalised medicine are increasingly being applied to the management of patients with thyroid cancer. Advances in molecular medicine and the development of prognostic nomograms[40] will facilitate this process. However, for the foreseeable future, conventional clinical and histopathological parameters remain the principal tools on which management decisions have to be based.

The scoring and prognostic systems described above are helpful in stratifying patients, though they have evolved not only for clinical management but also for design and analysis of clinical trials or retrospective clinical studies and for cancer registration purposes.[41]

Post-operative staging. TNM staging—Post-operative TNM staging predicts the risk of death from disease, and is a valuable indicator of overall prognosis (Table 2.1). However, it does not take into account individual responses to treatment, which may alter prognosis, and it does not predict recurrence.

Table 2.1. The TNM system (7th edition)[47]

(a) Classification according to tumour, nodes and metastases

Primary tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤2 cm in greatest dimension limited to the thyroid
T1a	Tumour ≤1 cm, limited to the thyroid
T1b	Tumour >1 cm but ≤2 cm in greatest dimension, limited to the thyroid
T2	Tumour >2 cm but ≤4 cm in greatest dimension, limited to the thyroid
T3	Tumour >4 cm in greatest dimension limited to the thyroid or any tumour with minimal extra-thyroidal extension (e.g. extension to sternothyroid muscle or perithyroid soft tissues)
T4a	Tumour of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, oesophagus, or recurrent laryngeal nerve
T4b	Tumour invades prevertebral fascia or encases carotid artery or mediastinal vessels

All anaplastic carcinomas are considered pT4 tumours

pT4a	Anaplastic carcinoma limited to thyroid
pT4b	Anaplastic carcinoma extends beyond thyroid capsule

Multifocal tumours (≥2 foci) of all histological types should be designated (m), the largest focus determining the classification, e.g. pT2(m)

Regional lymph nodes (cervical or upper mediastinal)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastases to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b	Metastases to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)

Distant metastases

M0	No distant metastasis
M1	Distant metastasis

Residual tumour

RX	Cannot assess presence of residual primary tumour
R0	No residual primary tumour
R1	Microscopic residual primary tumour
R2	Macroscopic residual primary tumour

(b) Papillary or follicular carcinoma staging

Papillary or follicular thyroid tumours, in a person younger than 45 years

Stage I: This stage describes a tumour (any T) with or without spread to lymph nodes (any N) and no distant metastasis (M0)

Stage II: This stage describes a tumour (any T) with any metastasis (M1) regardless of whether it has spread to the lymph nodes (any N)

Papillary or follicular thyroid tumours, in a person 45 years and older

Stage I: This stage describes any small tumour (T1) with no spread to lymph nodes (N0) and no metastasis (M0)

Stage II: This stage describes a larger, non-invasive tumour (T2) with no spread to lymph nodes (N0) and no metastasis (M0)

Table 2.1. (continued)

(b) Papillary or follicular carcinoma staging

Stage III: This stage describes a tumour larger than 4 cm but contained in the thyroid (T3) with no spread to lymph nodes (N0) and no metastasis (M0). Or, any localized tumour (T1–3) with spread to the central compartment of lymph nodes (N1a), but no distant spread (M0)

Stage IVA: This stage describes a tumour that has spread to nearby structures (T4a), regardless of whether it has spread to the lymph nodes (any N), but it has not spread to distant places (M0). Or, this describes a localized tumour (T1–3), with lymph node spread beyond the central compartment (N1b), but no distant spread (M0)

Stage IVB: This stage describes a tumour that has spread beyond nearby structures (T4b), regardless of spread to lymph nodes (any N), but no distant spread (M0)

Stage IVC: This stage describes all tumours (any T, any N) when there is evidence of metastasis (M1)

(c) 10-year relative survival mortality rates for differentiated (papillary or follicular) thyroid cancer (adapted from[5]) (see also[28]).

Stage	10-year relative survival (%)
I	98·5
II	98·8
III	99·0
IVA	75·9
IVB	62·5
IVC	63

Post-operative risk stratification for risk of recurrence—A three tier system adapted from the American Thyroid Association (ATA) guidelines[48] may be used to assign risk for persistent or recurrent disease (Table 2.2). This is useful for determining

Table 2.2. Post-operative risk stratification for risk of recurrence of DTC (adapted from[48])

Low-risk patients have the following characteristics:
- No local or distant metastases
- All macroscopic tumour has been resected i.e. R0 or R1 resection (pathological definition)
- No tumour invasion of loco-regional tissues or structures
- The tumour does not have aggressive histology (tall cell, or columnar cell PTC, diffuse sclerosing PTC, poorly differentiated elements), or angioinvasion

Intermediate-risk patients have any of the following characteristics:
- Microscopic invasion of tumour into the perithyroidal soft tissues (T3) at initial surgery
- Cervical lymph node metastases (N1a or N1b)
- Tumour with aggressive histology (tall cell, or columnar cell PTC, diffuse sclerosing PTC, poorly differentiated elements) or angioinvasion

High-risk patients have any of the following characteristics:
- Extra-thyroidal invasion
- Incomplete macroscopic tumour resection (R2)
- Distant metastases (M1)

Table 2.3. Dynamic Risk Stratification: definitions of response to initial therapy of DTC (9–12 months after total thyroidectomy with R0 resection and subsequent RRA, adapted from[49])

Excellent response	Indeterminate response	Incomplete response
All the following • Suppressed and stimulated Tg < 1 μg/l* • Neck US without evidence of disease • Cross-sectional and/or nuclear medicine imaging negative (if performed)	Any of the following • Suppressed Tg < 1 μg/l* and stimulated Tg ≥1 and <10 μg/l* • Neck US with nonspecific changes or stable sub centimetre lymph nodes • Cross-sectional and/or nuclear medicine imaging with nonspecific changes, although not completely normal	Any of the following • Suppressed Tg≥1 μg/l* or stimulated Tg ≥ 10 μg/l* • Rising Tg values • Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging
Low risk	Intermediate risk	High risk

*Assumes absence of interference in the Tg assay.

whether patients should undergo radioiodine remnant ablation (RRA) (Chapter 9), and the intensity and method of follow up in the post-operative setting.

Dynamic risk stratification—For patients who have undergone total thyroidectomy with R0 resection and RRA, the 9–12 months post-RRA stimulated thyroglobulin (sTg), whole

Table 2.4. Examples of uncertain indications for interventions where **Personalised Decision Making** may be applied

Clinical scenario	Intervention for which the indication is uncertain	Additional risk factors to be considered, which may swing the balance in favour of the intervention
Papillary thyroid microcarcinoma (microPTC) with history of neck irradiation (Chapter 8.3)	Total thyroidectomy (*vs* hemithyroidectomy)	Size >0·5 cm; non-incidental; positron emission tomography (PET) positive;* poorly differentiated component; desmoplastic fibrosis and/or infiltrative growth pattern
Papillary thyroid cancer (PTC) >1–≤4 cm with no other adverse factors (patient younger than aged 45 years, no clinical or radiological evidence of lymph node or distant metastases, unifocal tumour, no angioinvasion, no extra-thyroidal invasion) (Chapter 7.6)		Size > 2 cm; PET positive*; poorly differentiated component; radiation-induced cancer
Oncocytic (Hürthle cell) microcarcinoma (Chapter 7.6)		
MicroPTC with any of the following (Chapter 8.2): (a) multifocal involving both lobes (c) minimal extra-thyroidal extension through the thyroid capsule (pT3)	Prophylactic central compartment node dissection (PCCND) (*vs* no PCCND)	Poorly differentiated component; desmoplastic fibrosis and/or infiltrative growth pattern;
PTC <1 cm who have no clinical / radiological evidence of lymph node involvement, but have any of the following characteristics (Chapter 7.6): (a) age ≥45 years (b) multifocal (c) minimal-extra thyroidal extension through the thyroid capsule (pT3)		Poorly differentiated component; angioinvasion
Oncocytic (Hürthle cell) follicular carcinoma (Chapter 7.6)		Tumour >5 cm; age >80 years, male gender
MicroPTC with any of the following (Chapter 8.2): (a)minimal extra-thyroidal extension through the thyroid capsule (pT3) (b) Lymph node metastases resected surgically	Radioiodine Remnant Ablation (RRA) (*vs* no RRA)	Unfavourable histological cell type (tall cell, columnar, insular, diffuse sclerosing papillary cancer, poorly differentiated elements); multiple metastatic lymph nodes (>5) resected metastatic lymph nodes large in size (>6 mm), high ratio of positive to negative nodes (>0·7); extra-capsular nodal involvement[50–55]

Table 2.4. (continued)

Clinical scenario	Intervention for which the indication is uncertain	Additional risk factors to be considered, which may swing the balance in favour of the intervention
Patients with tumour size >1–≤4 cm, no distant metastases, minimal extra-thyroidal extension through the thyroid capsule (pT3), R0/1 resection, lymph node metastases resected surgically (Chapter 9.1)		Tumour size > 2 cm; presence of unfavourable histological cell type (tall cell or columnar cell PTC, diffuse sclerosing papillary cancer, poorly differentiated elements); widely invasive histology; multiple metastatic lymph nodes (>5) resected metastatic lymph nodes large in size (>6 mm), high ratio of positive to negative nodes (>0·7); extra-capsular nodal involvement

PET-CT is not an appropriate primary investigation for PTC, but when thyroid cancers are discovered coincidentally on a PET-CT, they tend to behave more aggressively.[56]

body scan (WBS) (if performed) and neck ultrasound (US), will allow potential modification of the initial static risk estimate based on the patient's response to RRA. Using a combination of clinicopathological factors with treatment response criteria allows a more personalised approach to treatment, follow up and prognostication[49] (Table 2.3). This will facilitate follow up as the majority of patients will have achieved an excellent response and TSH suppression can be relaxed (Chapter 11), allowing the TSH concentration to rise to the low-normal range. Annual Tg assessment can be carried out without stimulation and follow up intervals can be extended (Chapter 13).

i The TNM classification (7th edition)[47] (Table 2.1) is recommended[38,43–45] (**4, D**).
Key recommendation

ii The ATA post-operative risk stratification for risk of recurrence shown in Table 2.2 is recommended (adapted from[48]) (**4, C**).
Key recommendation

iii Allocation to one of three response groups after Dynamic Risk Stratification (Table 2.3) is recommended (**2-, C**).
Key recommendation

2.4. Managing uncertainty and Personalised Decision Making

Clear recommendations for or against treatments are possible for specific patient groups, but in many cases there is uncertainty. Both clinicians and patients can feel uncomfortable dealing with uncertainty. However, if handled appropriately, this process can become a positive experience and increase confidence about making the right choice. To achieve this, patient and clinician need to have adequate time for discussion, the opportunity for relatives or other third parties to participate in the discussion should be given if desired by the patient, time to reflect should be allowed, good quality information about the implications of the different options should be made available, and the responsible clinician should lead and guide the patient' choice using his/her expert knowledge.

i When the evidence for or against a treatment is inconclusive and no well designed, peer reviewed randomised or prospective national or institutional studies are ongoing to address this issue or if available, declined by the patient, these guidelines recommend a personalised approach to decision making (**Personalised Decision Making**) (**4, D**).
Key recommendation

Personalised Decision Making involves clinicians and patients working together to find a solution, that best suits the circumstances of the individual patient. This process consists of:

a Discussion in the multi-disciplinary team (MDT) meeting, where the evidence for and against an intervention is weighted and potential benefits and detrimental effects considered
b Consideration of risk factors for tumour-specific mortality and recurrence that apply to the intervention. Within this group of patients there is a spectrum of risk defined by clinical and histopathological parameters. Generally the greater the number of risk factors the stronger is the case in favour of the intervention
c Consideration of the patient's comorbidities, personal circumstances and values
d Use of the 'Shared Decision Making' model whenever appropriate[46]

Examples of uncertainty in decision making where **Personalised Decision Making** may be applied are shown in Table 2.4.

References

1 Benbassat, C.A., Mechlis-Frish, S. & Hirsch, D. (2006) Clinicopathological characteristics and long-term outcome in patients with distant metastases from differentiated thyroid cancer. *World Journal of Surgery*, **30**, 1088–1095.

2 Durante, C., Haddy, N., Baudin, E. *et al.* (2006) Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *Journal of Clinical Endocrinology and Metabolism*, **91**, 2892–2899.

3 Lee, J. & Soh, E.Y. (2010) Differentiated thyroid carcinoma presenting with distant metastasis at initial diagnosis: clinical outcomes and prognostic factors. *Annals of Surgery*, **251**, 114–119.

4 Mazzaferri, E.L. (1999) An overview of the management of papillary and follicular thyroid carcinoma. *Thyroid*, **9**, 421–427.

5 Verburg, F.A., Mäder, U., Tanase, K. *et al.* (2013) Life expectancy is reduced in differentiated thyroid cancer patients ≥ 45 years old with extensive local tumour invasion, lateral lymph node, or distant metastases at diagnosis and normal in all other DTC patients. *Journal of Clinical Endocrinology and Metabolism*, **98**, 172–180.

6 Mazzaferri, E.L. & Jhiang, S.M. (1994) Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *American Journal of Medicine*, **97**, 418–428.

7 Carcangiu, M.L., Zampi, G., Pupi, A. *et al.* (1985) Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy. *Cancer*, **55**, 805–828.

8 Simpson, W.J., McKinney, S.E., Carruthers, J.S. *et al.* (1987) Papillary and follicular thyroid cancer: prognostic factors in 1578 patients. *American Journal of Medicine*, **83**, 479–488.

9 Tubiana, M., Schlumberger, M., Rougier, P. *et al.* (1985) Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. *Cancer*, **55**, 794–804.

10 Akslen, L.A., Haldorsen, T., Thoresen, S.O. *et al.* (1991) Survival and causes of death in thyroid cancer: a population-based study of 2479 cases from Norway. *Cancer Research*, **51**, 1234–1241.

11 Hay, I.D. (1990) Papillary thyroid carcinoma. *Endocrinology and Metabolism Clinics of North America*, **19**, 545–576.

12 Furmanchuk, A.W., Averkin, J.I., Egloff, B. *et al.* (1992) Pathomorphological findings in thyroid cancers of children from the Republic of Belarus: a study of 86 cases occurring between 1986 ('post-Chernobyl') and 1991. *Histopathology*, **21**, 401–408.

13 Schlumberger, M., De Vathaire, F., Travagli, J.P. *et al.* (1987) Differentiated thyroid carcinoma in childhood: long term follow-up of 72 patients. *Journal of Clinical Endocrinology and Metabolism*, **65**, 1088–1094.

14 Yang, L., Shen, W. & Sakamoto, N. (2013) Population-based study evaluating and predicting the probability of death resulting from thyroid cancer and other causes among patients with thyroid cancer. *Journal of Clinical Oncology*, **31**, 468–474.

15 Oyer, S.L., Smith, V.A. & Lentsch, E.J. (2012) Reevaluating the prognostic significance of age in differentiated thyroid cancer. *Otolaryngology – Head and Neck Surgery*, **147**, 221–226.

16 Cady, B. & Rossi, R. (1988) An expanded view of risk group definition in differentiated thyroid carcinoma. *Surgery*, **104**, 947–953.

17 Brennan, M., Bergstralh, E.H., Heerden, J.A. *et al.* (1991) Follicular thyroid cancer treated at the Mayo Clinic 1946–1970. Initial manifestation, pathologic findings, therapy and outcome. *Mayo Clinic Proceedings*, **66**, 11–22.

18 Emerick, G.T., Duh, Q.Y., Siperstein, A.E. *et al.* (1993) Diagnosis, treatment and outcome of follicular thyroid carcinoma. *Cancer*, **72**, 3287–3295.

19 Donohue, J.H., Goldfien, S.D., Miller, T.R. *et al.* (1984) Do the prognoses of papillary and follicular thyroid carcinomas differ? *American Journal of Surgery*, **148**, 168–173.

20 Evans, H.L. (1986) Columnar-cell carcinoma of the thyroid. A report of two cases of an aggressive variant of thyroid carcinoma. *American Journal of Clinical Pathology*, **85**, 77–80.

21 Herrera, M.F., Hay, I.D., Wu, P.S. *et al.* (1992) Hurthle cell (oxyphilic) papillary thyroid carcinoma: a variant with more aggressive biologic behavior. *World Journal of Surgery*, **16**, 669–674.

22 Akslen, L.A. & LiVolsi, V.A. (2000) Prognostic significance of histologic grading compared with subclassification of papillary thyroid carcinoma. *Cancer*, **88**, 1902–1908.

23 Rosai, J., Zampi, G. & Carcangiu, M.L. (1983) Papillary carcinoma of the thyroid. A discussion of its several morphologic expressions, with particular emphasis on the follicular variant. *American Journal of Surgical Pathology*, **7**, 809–817.

24 Kazaure, H.S., Roman, S.A. & Sosa, J.A. (2012) Aggressive variants of papillary thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients. *Annals of Surgical Oncology*, **19**, 1874–1880.

25 Hay, I.D., Bergstralh, E.J., Goellner, J.R. *et al.* (1993) Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery*, **114**, 1050–1058.

26 Lang, W., Choritz, H. & Hundeshagen, H. (1986) Risk factors in follicular thyroid carcinomas. A retrospective follow-up study covering a 14-year period with emphasis on morphological findings. *American Journal of Surgical Pathology*, **10**, 246–255.

27 DeGroot, L.J., Kaplan, E.L., Shukla, M.S. *et al.* (1995) Morbidity and mortality in follicular thyroid cancer. *Journal of Clinical Endocrinology and Metabolism*, **80**, 2946–2953.

28 Hundahl, S.A., Fleming, I.D., Fremgen, A.M. *et al.* (1998) A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995. *Cancer*, **83**, 2638–2648.

29 Kazaure, H.S., Roman, S.A. & Sosa, J.A. (2012) Insular thyroid cancer: a population-level analysis of patient characteristics and predictors of survival. *Cancer*, **118**, 3260–3267.

30 Yamashita, H., Noguchi, S., Murakami, N. *et al.* (1997) Extracapsular invasion of lymph node metastasis is an indicator of distant metastasis and poor prognosis in patients with thyroid papillary carcinoma. *Cancer*, **80**, 2268–2272.

31 DeGroot, L.J., Kaplan, E.L., McCormick, M. *et al.* (1990) Natural history, treatment and course of papillary thyroid cancer. *Journal of Clinical Endocrinology and Metabolism*, **71**, 414–424.

32 Smith, V.A., Sessions, R.B. & Lentsch, E.J. (2012) Cervical lymph node metastasis and papillary thyroid carcinoma: does the compartment involved affect survival? Experience from the SEER database. *Journal of Surgical Oncology*, **106**, 357–3562.

33 Dinneen, S.F., Valimaki, M.J., Bergstralh, E.J. *et al.* (1995) Distant metastases in papillary thyroid carcinoma: 100 cases observed at one institution during 5 decades. *Journal of Clinical Endocrinology and Metabolism*, **80**, 2041–2045.

34 Hoie, J., Stenwig, A.E., Kullmann, G. *et al.* (1988) Distant metastases in papillary thyroid cancer. A review of 91 patients. *Cancer*, **61**, 1–6.

35 Pacini, F., Cetani, F., Miccoli, P. *et al.* (1994) Outcome of 309 patients with metastatic differentiated thyroid carcinoma treated with radioiodine. *World Journal of Surgery*, **18**, 600–604.

36 Wong, R.M., Catherine Bresee, C. & Braunstein, G.D. (2013) Comparison with published systems of a new staging system for papillary and follicular thyroid carcinoma. *Thyroid*, **23**, 566–574.
37 Pathak, K.A., Mazurat, A., Lambert, P. *et al.* (2013) Prognostic nomograms to predict oncological outcome of thyroid cancers. *Journal of Clinical Endocrinology and Metabolism*, **98**, 4768–4775.
38 Loh, K.C., Greenspan, F.S., Gee, L. *et al.* (1997) Pathological tumor-node-metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. *Journal of Clinical Endocrinology and Metabolism*, **82**, 3553–3562.
39 D'Avanzo, A., Ituarte, P., Treseler, P. *et al.* (2004) Prognostic scoring systems in patients with follicular thyroid cancer: a comparison of different staging systems in predicting the patient outcome. *Thyroid*, **14**, 453–458.
40 Ross, D.S. (2013) Predicting outcome in patients with thyroid cancer. *JCEM*, **98**, 4673–4675.
41 Sherman, S.I., Brierley, J.D., Sperling, M. *et al.* (1998) Prospective multicenter study of thyroid carcinoma treatment, initial analysis of staging and outcome. *Cancer*, **83**, 1012–1021.
42 Castagna, M.G., Maino, F., Cipri, C. *et al.* (2011) Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients. *European Journal of Endocrinology*, **165**, 441–446.
43 Wittekind, C., Meyer, H. & Bootz, F. (eds). (1997) TNM. Klassifikation maligner Tumoren, 5th edn. Springer, Berlin.
44 Brierley, J.D. & Panzarella, T. (1997) A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. *Cancer*, **79**, 2414–2423.
45 Passler, C., Prager, G., Scheuba, C. *et al.* (2003) Application of staging systems for differentiated thyroid carcinoma in an endemic goiter region with iodine substitution. *Annals of Surgery*, **237**, 227–234.
46 Politi, M.C., Dizon, D.S., Frosch, D.L. *et al.* (2013) Importance of clarifying patients' desired role in shared decision making to match their level of engagement with their preferences. *BMJ*, **347**, f7066.
47 Sobin, L.H., Gospodarowicz, M.K. & Wittekind, C. (2009) TNM Classification of Malignant Tumours (7th edn). Wiley-Blackwell, Oxford.
48 Cooper, D.S., Doherty, G.M., Haugen, B.R. *et al.* (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*, **19**, 1167–1214.
49 Tuttle, R.M., Tala, H., Shah, J. *et al.* (2010) Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. *Thyroid*, **20**, 1341–1349.
50 Vas Nunes, J.H., Clark, J.R., Gao, K. *et al.* (2013) Prognostic implications of lymph node yield and lymph node ratio in papillary thyroid carcinoma. *Thyroid*, **23**, 811–816.
51 Rajeev, P., Ahmed, S., Ezzat, T.M. *et al.* (2013) The number of positive lymph nodes in the central compartment has prognostic impact in papillary thyroid carcinoma. *Langenbeck's Archives of Surgery*, **398**, 377–382.
52 Lang, B.H., Tang, A.H., Wong, K.P. *et al.* (2012) Significance of size of lymph node metastasis on postsurgical stimulated thyroglobulin levels after prophylactic unilateral central neck dissection in papillary thyroid carcinoma. *Annals of Surgical Oncology*, **19**, 3472–3478.
53 Lee, Y.S., Lim, Y.S., Lee, J.C. *et al.* (2013) Nodal status of central lymph nodes as a negative prognostic factor for papillary thyroid carcinoma. *Journal of Surgical Oncology*, **107**, 777–782.
54 Schneider, D.F., Mazeh, H., Chen, H. *et al.* (2013) Lymph node ratio predicts recurrence in papillary thyroid cancer. *The Oncologist*, **18**, 157–162.
55 Randolph, G.W., Duh, Q.Y., Heller, K.S. *et al.* (2012) The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid*, **22**, 1144–1152.
56 Mosci, C. & Iagaru, A. (2011) PET/CT imaging of thyroid cancer. *Clinical Nuclear Medicine*, **36**, e180–e185.

CHAPTER 3

3 Presentation, diagnosis and referral

Thyroid nodules are common in adults and may be detected by palpation in 3–7% of patients.[1] The prevalence may be as high as 70% or more if sensitive imaging such as ultrasonography is used (Chapter 4). 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 general practitioner (GP) (Chapter 21).

3.1. Cancer waiting times

Referrals for suspected cancer are required to be seen in secondary care within 2 weeks, as set out in the Department of Health Cancer Plan document, *Cancer waiting targets: a guide.*[2] Specialists in secondary care have a maximum of 31 days from 'decision to treat' to first definitive treatment and a maximum of 62 days from urgent GP referral for suspected cancer to first definitive treatment (Fig. 3.1).

In the case of thyroid nodules, the time of 'decision to treat' is when a decision to proceed to thyroidectomy is made after discussion with the patient. Decisions to treat thyroid cancers should follow multidisciplinary team (MDT) discussions, in accordance with the measures of the National Cancer Peer Review Programme.[3] The date of first definitive treatment is the date of thyroidectomy (either hemithyroidectomy or total thyroidectomy).

The most common presentation of thyroid cancer is a newly discovered 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 of those who harbour a malignancy is generally excellent.

i 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 (see 3.2 below), and that optimum care can be delivered by adopting a target of 4 weeks from referral to first assessment in secondary care for all other thyroid nodules (**4, D**).

ii Hospitals providing secondary care for patients with suspected thyroid cancer should develop well-defined and streamlined pathways of referral and care. Designated diagnostic clinics with appropriate resources for patients with thyroid masses are desirable (**4, D**).

3.2. 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. GPs 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 (**4, D**):

- Patients with a history of a nodule or goitre which has not changed for several years and who have no other worrying features (i.e. adult patient, no history of neck irradiation, no family history of thyroid cancer, no palpable cervical lymphadenopathy, no stridor or voice change).
- Patients with a non-palpable asymptomatic nodule <1 cm in diameter discovered incidentally on neck ultrasound (US) USS / CT /MRI without other worrying features.

Patients who should be referred non-urgently (**4, D**):

- Patients with nodules who have abnormal thyroid function tests (TFTs). These patients should be referred to an endocrinologist; thyroid cancer is very rare in this group.
- Patients with a history of sudden onset of pain in a thyroid lump (likely to have bled into a benign thyroid cyst).

Symptoms needing urgent referral (2-week rule)[2] (**4, D**):

- Unexplained hoarseness or voice changes associated with a goitre
- Thyroid nodule in a child
- Cervical lymphadenopathy associated with a thyroid mass (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 (**4, D**):

- *Stridor* associated with a thyroid mass.

3.3. Physical examination

i The patient should have a full examination focusing 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 (**4, D**).

3.4. Appropriate investigations pending hospital appointment

i TFTs should be requested by the GP (**4, D**).

ii Euthyroid patients with a thyroid nodule may have thyroid cancer and should be referred to a member of a multidisciplinary thyroid cancer team (see section 3.5 below).**National Cancer Programme, measure 11-1D-103i**[3]

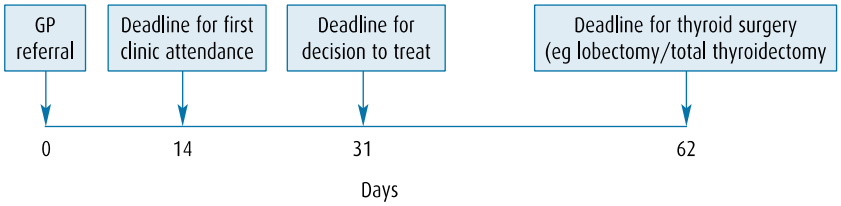


Fig. 3.1 Thyroid Cancer waiting times.

i Patients with hyper- or hypothyroidism and a nodular goitre without suspicious features should be referred routinely to an endocrinologist (**4, D**).

ii 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 cancer[4] and is not recommended (**2+, C**).

3.5. Who to refer to?

i Patients should be referred to a surgeon, endocrinologist, or nuclear medicine physician who has a specialist interest in thyroid cancer and is a core member of the MDT.
National Cancer Peer Review Programme, measure 11-1D-103i[3]
Key Recommendation

ii The local cancer centre or cancer unit should provide clear guidance to GPs on referral pathways to secondary care.
National Cancer Peer Review Programme, measure 11-1D-102i[3]

3.6. The role of the multidisciplinary team

i All patients with thyroid cancer should be seen within an MDT framework
National Cancer Peer Review Programme, measure 11-1D-103i[3]

ii Patients with suspected thyroid cancer will usually be seen initially by an individual member of the MDT, who will be working according to guidelines (**4, D**).

iii The treatment plan and care of each newly diagnosed patient should be discussed and supervised by a core team (physician / surgeon) in consultation with other members of the MDT. This discussion should be recorded in the patient's notes (**4, D**).

iv Close communication between members of the MDT is key for delivering optimal care and a combined clinic is the preferred format (**4, D**).

v The management of MTC is best delivered by a dedicated group of clinicians within the MDT who have special expertise in this complex disease (**4, D**).

3.7. Hospital investigations

While the decision to proceed with investigations will be appropriate in most cases, there are occasions when no further investigation may be a better choice. Co-morbidities and other factors including patient choice are important in making this judgment. Circumstances where further investigation of thyroid nodules for malignancy may not be in the patient's best interests include:

- Age, comorbidities or other patient characteristics pose a significant limitation to patient's life expectancy, so that diagnosing and treating a thyroid cancer is likely to expose the patient to more risk than benefit.
- Clear history of a nodule that has not changed over many years in patients who are not concerned and are not at high risk of thyroid cancer (no history of neck irradiation, no family history of thyroid cancer) and have no suspicious features on clinical examination.
- Patients with thyroid nodules who have been investigated in the past with negative results and give a clear history of no change in the nodule and have no suspicious features on clinical examination.
- Patients with toxic multinodular goitre or toxic nodule who give no history of recent change in the goitre and have no suspicious features on clinical examination.

Clinical features which are statistically associated with increased probability of malignancy include:

- Age less than 20 or older than 60 years[4];
- Firmness of the nodule on palpation;
- Rapid growth;
- Fixation to adjacent structures;
- Vocal cord paralysis;
- Regional lymphadenopathy;
- History of neck irradiation;
- Family history of thyroid cancer.[4]

Essential assessments.

i Thorough history and examination (**4, D**).

ii US is an extremely sensitive examination for thyroid nodules. It can be specific for the diagnosis of thyroid carcinoma (particularly papillary carcinoma), and aids decision making about which nodules to perform FNAC. US also consistently increases the yield of diagnostic FNACs (Chapter 4).
Good Practice Point ☑
Key recommendation

iii Review of TFTs[5] (**2+, C**).

iv Note that the measurement of serum thyroglobulin (Tg) before thyroidectomy has no

diagnostic or prognostic value and should not be undertaken[5] (**3, D**).

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 on a background of Hashimoto's thyroiditis).
ii Magnetic resonance imaging (MRI) or computed tomography (CT) scanning is indicated when the limits of the goitre cannot be determined clinically or for fixed tumours or in patients with haemoptysis. If appropriate, it is important to avoid the use of iodinated media when undertaking CT scans as these may reduce the subsequent radioiodine uptake by thyroid tissue for a minimum of 2 months (Chapter 9.2). Gadolinium-enhanced MRI may provide useful information without compromising subsequent radioiodine uptake by any remaining thyroid tissue.
iii Measurement of basal plasma calcitonin and carcinoembryonic antigen (CEA) may be useful if medullary thyroid cancer (MTC) is suspected[6,7] but is not recommended routinely for all thyroid nodules (**4, D**).
iv Flow-volume loop studies may be indicated if upper airways obstruction is suspected[8] (**4, D**).
v Radioisotope studies are non-specific for thyroid cancer and therefore not recommended for diagnosis[9,10] (**4, D**).
vi Open biopsy is rarely indicated. 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 US guidance is recommended (**4, D**).

3.8. Communication and patient information prior to investigations

i Undergoing investigations for a thyroid lump may be a stressful experience for the patient, exacerbated by inadequate or misleading information and by excessive waiting times for tests. High quality information about the individual's risk of having thyroid cancer and the complexities and limitations of diagnostic tests to exclude thyroid cancer should be provided to patients (**4, D**).

Key recommendation

ii Patients undergoing investigation for thyroid nodules, need to understand that after completion of investigations, there may still be uncertainty about the nodule being benign or malignant and that the statistical outcome in most cases is a reduction of risk of having thyroid cancer from 5–10% to 1% or less (**4, D**).
iii Patients referred for US, or FNAC should have an understanding of why these investigations are being performed (**4, D**).
iv Provision of information in the form of leaflets (Appendix 4, Patient Information Leaflets 1 and 2) to complement consultations is recommended (**4, D**).

3.9. Communicating the diagnosis of thyroid cancer

Informing the primary care team.

i The GP should be informed (by telephone or fax) within 24 h 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 (**4, D**).
ii Subsequently any alterations in prognosis, management or drug treatment should be communicated promptly (**4, D**).

Informing the patient.

i The patient should be informed of the diagnosis of cancer by a member of the MDT in person, preferably in the presence of a nurse during a private, uninterrupted consultation. Patients should be offered the opportunity of having a relative or friend present during the consultation. Facilities should be available for this to be done during a private, uninterrupted consultation (**4, D**).

Key recommendation

ii Written information concerning thyroid cancer and its treatment and possible complications should be available to the patient (Appendix 4, patient information leaflets 1–7) (**4, D**).
iii A prognosis should not be offered before adequate staging information is available (**4, D**).
iv Patients may have difficulty assimilating all this information at a single consultation and an opportunity for further explanation/discussion should be offered (**4, D**).

References

1 Hegedus, L., Bonnema, S.J. & Bennedbaek, F.N. (2003) Management of simple nodular goiter: current status and future perspectives. *Endocrine Reviews*, **24**, 102–132.
2 Department of Health. (2006) Cancer Waiting Times: A Guide (Version 5). DH, London. Available from: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_06306761.
3 http://www.mycancertreatment.nhs.uk/wpcontent/themes/mct/uploads/2012/09/resources_measures_HeadNeck_Measures_April2011.pdf.
4 Kumar, H., Daykin, J., Holder, R. *et al.* (1999) Gender, clinical findings and serum thyrotropin measurements in the prediction of thyroid neoplasia in 1005 patients presenting with thyroid enlargement and investigated by fine needle aspiration cytology (FNAC). *Thyroid*, **9**, 1105–1109.
5 Association of Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation. (2006) UK Guidelines for the Use of Thyroid Function Tests. ACB, London.
6 Elisei, R., Bottici, V., Luchetti, F. *et al.* (2004) Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders. *Journal of Clinical Endocrinology and Metabolism*, **89**, 163–168.
7 Rieu, M., Lame, M.C., Richard, A. *et al.* (1995) Prevalence of sporadic medullary thyroid carcinoma: the importance of

routine measurement of serum calcitonin in the diagnostic evaluation of thyroid nodules. *Clinical Endocrinology*, **42**, 453–460.

8 Gittoes, N.J., Miller, M.R., Daykin, J. *et al.* (1996) Upper airways obstruction in 153 consecutive patients presenting with thyroid enlargement. *BMJ*, **312**, 484.

9 Rojeski, M.T. & Gharib, H. (1985) Nodular thyroid disease: evaluation and management. *New England Journal of Medicine*, **313**, 428–436.

10 Giuffrida, D. & Gharib, H. (1995) Controversies in the management of cold, hot and occult thyroid nodules. *American Journal of Medicine*, **99**, 642–650.

CHAPTER 4

4 Ultrasound assessment of thyroid nodules

Sonographically a thyroid nodule is a discrete lesion, distinguishable from the adjacent normal thyroid parenchyma. While thyroid nodules are found on clinical examination in 3–7% of the adult population, the incidence of detectable nodules on ultrasound (US) examination is between 30% and 70% and increases progressively with age.[1]

While size of the tumour has major consequences in staging and prognosis of thyroid cancer (Chapter 2), the size of a thyroid nodule, correlates poorly with the risk of malignancy.

4.1. Role of US in the investigation of thyroid nodules

US is an extremely sensitive examination for thyroid nodules. It can be specific for the diagnosis of thyroid carcinoma (particularly papillary carcinoma), and aids decision-making about which nodules to perform fine-needle aspiration cytology (FNAC).[2] US also consistently increases the yield of diagnostic FNAC.[3]

i All patients being investigated for possible thyroid cancer should undergo an US of the neck in secondary care by an appropriate, competent practitioner.
Good Practice Point ☑

ii The information derived from US of thyroid nodules should always be interpreted in the context of the individual patient's clinical picture (and when available, cytology findings).
Good Practice Point ☑

4.2. Benign and malignant US features of thyroid nodules

US features indicative of benign or malignant nodules are described in Table 4.1. No single US feature is diagnostic. Several retrospective series indicate that US characteristics of a nodule can be used reliably to detect malignancy.[1,2,4] The Kim criteria provide the greatest sensitivity,[5] while the American Association of Clinical Endocrinologists guidelines have the highest specificity[6,7] (Table 4.2). The Society of Radiologists in Ultrasound criteria, which rely primarily on size, are least accurate in the prediction of malignancy.[1] Multiple operators can achieve concordant results following training in the detection of the relevant signs.[2] A graphic presentation of the recognised signs that can be used to classify thyroid nodules is shown in Fig. 4.1. This allows Radiologists to use an US (U) classification (U1–U5). The use of such a classification system for the prediction of malignancy helps to determine whether a FNAC should be performed.[3–5,8,9]

i US signs should be used in summation to identify nodules that may be malignant and to guide FNAC of such lesions (**2++**, **B**).

ii The use of the U1–U5 scoring/grading system is recommended for assessing risk of malignancy and guiding FNAC (**2+**, **C**).
Key Recommendation

4.3. Selection of nodules for FNAC

Despite size of a nodule being used as a criterion in some guidelines, the evidence does not support size as a reliable indicator of malignancy.[5,8–14] While there are some studies indicating that nodule size is associated with malignancy,[15–17] a larger body of evidence suggests that size is not specific in distinguishing benign from malignant thyroid nodules.[18–21] Furthermore, guidelines that have used size as a criterion for the differentiating between benign and malignant thyroid nodules, have been shown to lack accuracy, compared to guidelines that use nodule morphology as a criterion.[6] Predictive US signs continue to evolve: techniques such as elastography,[22] and other new signs can be incorporated easily into the U classification system outlined above.

Cystic change is invariably detected within benign nodules however can be seen infrequently, in thyroid malignancy. In solid/cystic nodules, analysis of the internal solid portion should be carried out. Specific signs for malignancy are eccentric location of the solid portion, a non-smooth margin, hypoechogenicity of the solid portion and microcalcification within the solid portion. The overall shape of the nodule ie taller than wide (AP > TR), or irregular overall shape are also relevant for solid/cystic nodules as a predictor of malignancy.[23]

The high sensitivity of US for the detection of papillary carcinoma can result in the finding of small (<1 cm) nodules that are suspicious for thyroid malignancy. In such cases extra thyroidal extension and associated metastatic lymphadenopathy will influence the decision as to whether or not to perform FNAC. When there is no evidence of extra thyroidal disease, or no associated high risk clinical history, the decision whether or not to perform FNAC will depend on the clinical picture, and the responsible clinician needs to make an appropriate judgment (supported by the MDT) about pursuing cytological confirmation, in order to avoid overtreatment of clinically insignificant micro-papillary thyroid carcinomas (microPTCs).[24]

i US appearances that are indicative of a benign nodule (U1–U2) should be regarded as reassuring not requiring fine needle aspiration cytology (FNAC), unless the patient has a statistically high risk of malignancy (Chapter 3.7) (**2++**, **B**).

Key Recommendation

ii If the US appearances are equivocal, indeterminate or suspicious of malignancy (U3–U5), an US guided FNAC should

Table 4.1.

US features indicative of benign nodule

- spongiform or honeycomb appearance (micro-cystic spaces with thin walls, comprising >50% of the nodule)[8]
- purely cystic nodule[3] and nodules with a cystic component containing colloid (hyper-echoic foci with a 'ring-down' sign)
- egg shell type calcification around the periphery of a nodule[34,35]
- iso-echoic or (mildly) hyper-echoic in relation to the surrounding normal thyroid tissue and typically with a surrounding hypo-echoic halo
- peripheral vascularity on colour flow or power Doppler[8,36]

US features indicative of malignant nodule

Papillary and medullary cancers:

- a solid hypo-echoic (i.e. hypo-echoic relative to the normal thyroid tissue) nodule, which may contain hyper-echoic foci (i.e. micro-calcification)[5,8]
- an irregular margin, intra nodular vascularity and absence of an associated halo
- a 'taller than wide' shape referring to Anterior/Posterior (AP > Transverse (TR) diameter when imaged in the axial plane. AP diameter >TR diameter increasing the likelihood of malignancy)[6]
- an irregular or spiculated margin and a 'taller than wide' shape have both been shown to have good Positive Predictive Value for malignant nodules[6]
- egg shell type calcification around the periphery of a nodule with a broken calcified rim where there is extension beyond the calcified rim of a hypo-echoic mass[6]

Follicular lesions:

- typically hyper-echoic and homogenous in echo texture with a well defined halo
- hypo-echogenicity and loss of the associated halo -associated with carcinoma

Table 4.2.

Kim Criteria: marked hypo-echogenicity, irregular or micro-lobulated margins, micro-calcification or 'taller-than-wide (AP > TR) (high sensitivity)[5]
American Association Clinical Endocrinologists Criteria: hypo- echoic nodule with one added feature such as irregular margins, length greater > width (AP>TR), micro- calcifications (high specificity)[7]
(**American**) **Society of Radiologists in Ultrasound**: 1 cm in diameter or larger with micro-calcifications, 1·5 cm in diameter or larger: solid or has coarse calcifications, 2 cm in diameter or larger: mixed solid and cystic components/nodule undergone substantial growth or associated with abnormal cervical lymph nodes (least accurate)[1]

follow[10] (**2++**, **B**).

Key Recommendation

iii Any abnormal lymph node in the neck should undergo FNAC to facilitate accurate diagnosis/staging (**2++**, **B**).

4.4. Radiology reporting

i If a nodule is being assessed by US, the practitioner (be they a sonographer, surgeon, endocrinologist or radiologist) should be competent in identifying the characteristic signs that can allow a differentiation of thyroid nodules (i.e. either benign (U2), equivocal/indeterminate (U3), suspicious (U4) or malignant (U5) as outlined in the U classification, Fig. 4.1.

Good Practice Point ☑

ii A report should identify the various characteristics and give appropriate measurements of significant thyroid nodules/masses and the U score. In multinodular thyroids, the score for the most suspicious nodule should be recorded.

Good Practice Point ☑

iii Any retrosternal extension or tracheal deviation should be noted.

Good Practice Point ☑

iv When a malignancy is suspected a full assessment of the remainder of the neck for associated lymph node metastases is mandatory.

Good Practice Point ☑

4.5. Follow up of thyroid nodules

The follow up of thyroid nodules should depend upon the initial US appearances and associated cytology (Fig. 4.2).[25–28]

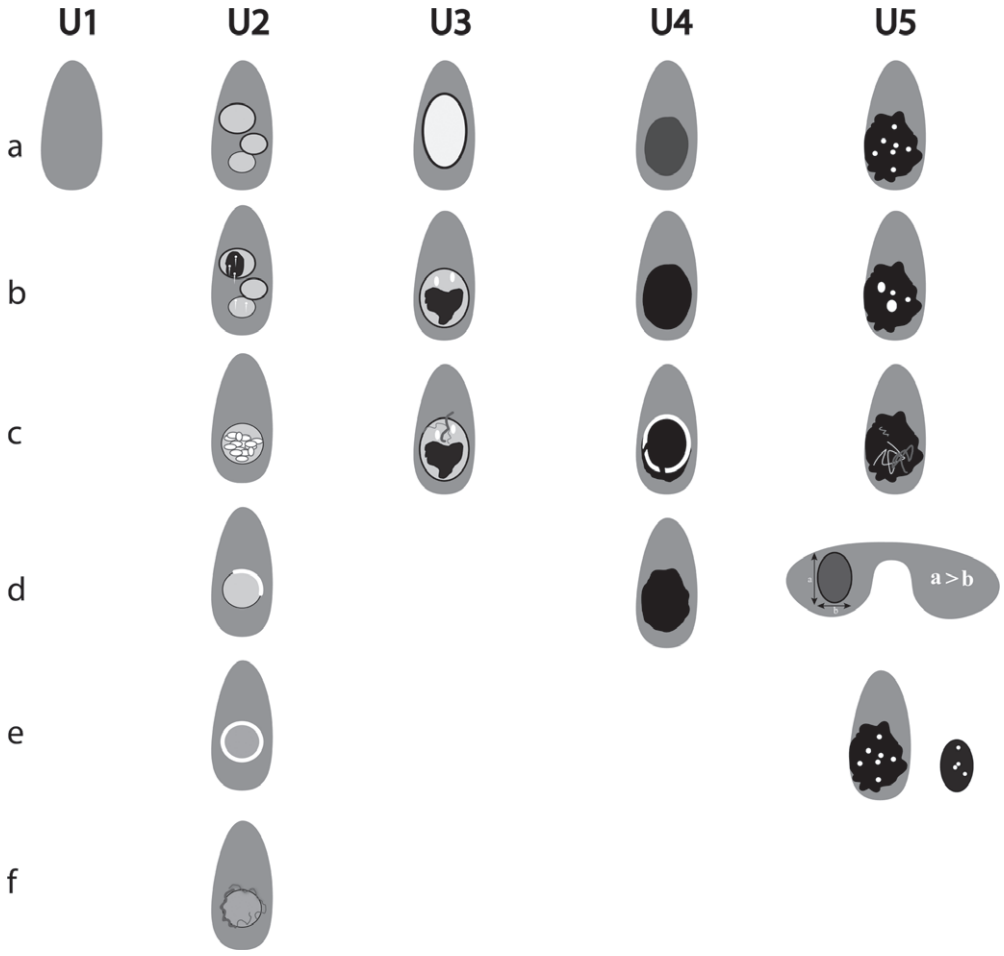
i Asymptomatic nodules with benign US characteristics and no clinical reasons to suspect a malignancy should be discharged from further follow-up. Routine ultrasound follow-up of nodules that are judged to be benign is not recommended (**2++**, **B**).

ii Nodules with benign (Thy2) cytology results and benign US characteristics do not need repeat FNAC, unless there is strong clinical suspicion of malignancy (**2+**, **C**).

iii Nodules with suspicious US appearances and inadequate cytology (Thy1), should undergo repeat US guided FNAC (**2++**, **B**).

iv Nodules with Thy2 cytology but indeterminate or suspicious US features should undergo repeat FNAC for confirmation. The rate of malignancy in this setting is significant, and evidence supports repeat cytological sampling[28] (**2++**, **B**).

Key Recommendation



U1. Normal.

U2. Benign:
(a) halo, iso-echoic / mildly hyper-echoic
(b) cystic change +/- ring down sign (colloid)
(c) micro- cystic / spongiform
(d & e) peripheral egg shell calcification
(f) peripheral vascularity.

U3. Indeterminate/Equivocal:
(a) homogenous, hyper-echoic (markedly), solid, halo (follicular lesion).
(b) ? hypo-echoic, equivocal echogenic foci, cystic change
(c) mixed/central vascularity.

U4. Suspicious:
(a) solid, hypo-echoic (cf thyroid)
(b) solid, very hypo-echoic (cf strap muscle)
(c) disrupted peripheral calcification, hypo-echoic
(d) lobulated outline

U5. Malignant
(a) solid, hypo-echoic, lobulated / irregular outline, micro-calcification. (? Papillary carcinoma)
(b) solid, hypo-echoic, lobulated/irregular outline, globular calcification (? Medullary carcinoma)
(c) intra-nodular vascularity
(d) shape (taller >wide) (AP>TR)
(e) characteristic associated lymphadenopathy

Fig. 4.1 Thyroid nodules-Ultrasound (U) Classification. Graphic compilation of the signs that can be used to differentiate benign from malignant nodules. These signs should be used to guide the decision as to whether or not to carry out a FNAB based on the likelihood of malignancy in a nodule.

v When there is discordance between level of clinical suspicion, FNAC or US appearances, management should be discussed in the MDT (**4**, **C**).

Atypical (Thy3a), follicular (Thy3f), suspicious (Thy4) and diagnostic (Thy5) cytology is discussed in Chapter 5.

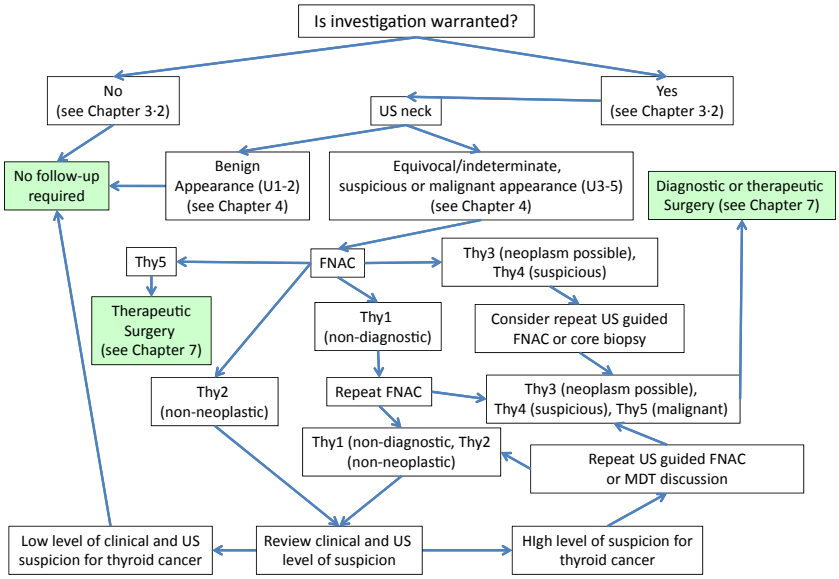


Fig. 4.2 Flow diagram describing investigation and management of thyroid nodules.

Table 4.3. Suggested features to consider/include in US reporting/assessment of thyroid nodules

Relevant Nodule Size:	
Nodule Composition:	Solid, cystic, mixed solid /cystic, micro-cystic/ spongiform
Cystic Component:	? Ring down sign – colloid
Echogenicity:	Markedly hypo-echoic, hypo-echoic, iso-echoic, hyper-echoic
Calcifications:	Micro-calcification, macro-calcification, rim/egg shell
Margin:	Well defined, irregular/lobulated, spiculated
Taller than Wide:	AP > TR: Y/N
Halo:	Regular/continuous, interrupted, absent
Colour flow:	Central, peripheral, mixed, none
Extent:	Retrosternal extension/tracheal deviation
Classification:	Benign (U2), equivocal/indeterminate (U3), suspicious (U4), malignant (U5)
Lymphadenopathy:	Suspected malignancy – ? metastases: anatomical location/levels
Biopsy:	FNAC/core biopsy, needle gauge, number of passes. Location of nodule biopsied Complications: Y/N

4.6. Incidental nodules

The inappropriate use and reporting of imaging can result in an epidemic of detected thyroid masses, the majority of which will be benign.[29,30] Any incidental nodule detected on US should be assessed using the criteria discussed above. Incidental nodules detected on computed tomography (CT) can be more problematic. CT underestimates nodularity and, contrary to US, no CT feature reliably distinguishes benign from malignant lesions.[31] If all nodules detected on CT were to be further investigated with US this would result in a significant resource issue. The exception to this is the incidentaloma detected on positron emission tomography (PET)-CT with focal[18] Fluoro-deoxy-glucose (FDG) activity, where the risk of malignancy is in excess of 30%.[32]

i A benign appearance on US should result in no further action other than reassurance for the patient (**2++**, **B**).

ii Incidentally detected nodules by CT should undergo clinical evaluation. In the majority of cases, no further assessment/investigation will be required. However if there are suspicious findings on CT (extra-capsular extension, tracheal invasion, associated suspicious lymphadenopathy), or the patient belongs to a high-risk group or if there is significant clinical concern, US assessment is recommended (**4**, **D**).

iii Nodules detected by PET-CT with focal FDG activity should be investigated with ultrasound and FNAC, unless disseminated disease is identified and the prognosis from an alternative malignancy would preclude further investigation (**1++**, **A**).

Key Recommendation

4.7. US Assessment by non-radiologists

Non-radiologists (surgeons, endocrinologists or sonographers) are increasingly involved in US assessment and US guided FNAC of thyroid nodules. Standards need to maintained by all professionals who undertake this responsibility.

i US assessment should be recorded with images captured on picture archiving and communications system (PACS), with a formal written report linked to the Radiology Information System.[33]

Good Practice Point ☑

ii Reporting should follow the diagnostic criteria as outlined in Table 4.3.

Good Practice Point ☑

iii Such services should be managed in conjunction with Radiology allowing supervision/advice to be sought when necessary.

Good Practice Point ☑

iv Training should follow the guidance outlined by the Royal College of Radiologists for other non-Radiology groups.[33]

Good Practice Point ☑

References

1 Frates, M.C., Benson, C.B. & Charbonneau, J.W. (2005) Management of thyroid nodules detected at US: society of radiologists in ultrasound consensus statement. *Radiology*, **237**, 794–800.

2 Hambly, N.M., Gonen, M. & Gerst, S.R. (2011) Implementation of Evidence-based guidelines for thyroid nodule biopsy: a model for establishment of practice standards. *American Journal of Roentgenology*, **196**, 655–660.

3 Cesur, M., Corapcioglu, D., Bulut, S. *et al.* (2006) Comparison of palpation guided fine needle aspiration biopsy to ultrasound guided fine needle aspiration biopsy in the evaluation of thyroid nodules. *Thyroid*, **16**, 555–561.

4 Lee, Y.H., Kim, D.W. & In, H.S. (2011) Differentiation between benign and malignant thyroid solid thyroid nodules using an ultrasound classification system. *Korean Journal of Radiology*, **12**, 559–567.

5 Kim, E.K., Park, C.S., Chung, W.Y. *et al.* (2002) New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. *American Journal of Roentgenology*, **178**, 687–691.

6 Ahn, S.S., Kim, E.-K. & Kang, D.R. (2010) Biopsy of thyroid nodules: comparison of three sets of guidelines. *American Journal of Roentgenology*, **194**, 31–37.

7 Gharib, H., Papini, E., Valcavi, R. *et al.* (2006) American Association of Clinical Endocrinologists and Associazone Medici Endocrinologi medical guidelines for the diagnosis and management of thyroid nodules. *Endocrine Practice*, **12**, 63–102.

8 Moon, W.J., Jung, S.L., Lee, J.H. *et al.* (2008) Benign and malignant thyroid nodules: US differentiation – Multicenter retrospective study. *Radiology*, **247**, 762–770.

9 Papini, E., Gugliemi, R., Bianchini, A. *et al.* (2002) Risk of malignancy in non-palpable thyroid nodules: predictive value of ultrasound and color-doppler features. *Journal of Clinical Endocrinology and Metabolism*, **87**, 1941–1946.

10 Moon, W.J., Maek, J.H. & Jung, S.L. (2011) Ultrasound and ultrasound based management of thyroid nodules: concensus statement and recommendations. *Korean Journal of Radiology*, **12**, 1–14.

11 Bonavita, J.A., Mayo, J., Babb, J. *et al.* (2009) Pattern recognition of benign nodules at ultrasound of the thyroid: which nodules can be left alone. *American Journal of Roentgenology*, **193**, 207–213.

12 Hoang, J., Lee, W.K., Lee, M. *et al.* (2007) US features of thyroid malignancy: pearls and pitfalls. *Radiographics*, **27**, 847–865.

13 Kim, M.J., Kim, E.-K. & Park, S. (2008) US guided FNA of thyroid nodules. Indications, techniques and results. *Radiographics*, **28**, 1869–1889.

14 Popowicz, B., Klencki, M., Lewinski, A. *et al.* (2009) The usefulness of sonographic features in selection of thyroid nodules for biopsy in relation to the nodule's size. *European Journal of Endocrinology*, **161**, 103–111.

15 Wharry, L.I., McCoy, K.L., Stang, M.T. *et al.* (2014) Thyroid nodules (≥4 cm): can ultrasound and cytology reliably exclude cancer? *World Journal of Surgery*, **38**, 614–621.

16 Smith-Bindman, R., Lebda, P., Feldstein, V.A. *et al.* (2013) Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: results of a population-based study. *JAMA Internal Medicine*, **173**, 1788–1796.

17 Kamran, S.C., Marqusee, E., Kim, M.I. *et al.* (2013) Thyroid nodule size and prediction of cancer. *Journal of Clinical Endocrinology and Metabolism*, **98**, 564–570.

18 Shrestha, M., Crothers, B.A. & Burch, H.B. (2012) The impact of thyroid nodule size on the risk of malignancy and accuracy of fine-needle aspiration: a 10-year study from a single institution. *Thyroid*, **22**, 1251–1256.

19 Mehanna, R., Murphy, M., McCarthy, J. *et al.* (2013) False negatives in thyroid cytology: impact of large nodule size and follicular variant of papillary carcinoma. *The Laryngoscope*, **123**, 1305–1309.

20 Albuja-Cruz, M.B., Goldfarb, M., Gondek, S.S. *et al.* (2013) Reliability of fine-needle aspiration for thyroid nodules greater than or equal to 4 cm. *Journal of Surgical Research*, **181**, 6–10.

21 McHenry, C.R., Huh, E.S. & Machekano, R.N. (2008) Is nodule size an independent predictor of thyroid malignancy? *Surgery*, **144**, 1062–1068.

22 Bojunga, J., Herrmann, E., Meyer, G. *et al.* (2010) Real-time elastography for the differentiation of benign and malignant thyroid nodules: a meta-analysis. *Thyroid*, **20**, 1145–1150.

23 Park, J.M., Yoonjung, C. & Kwag, H.J. (2012) Partially cystic thyroid nodules: ultrasound findings of malignancy. *Korean Journal of Radiology*, **13**, 530–535.

24 Brito, J.P., Morris, J.C. & Montori, V.M. (2013) Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours. *BMJ*, **347**, f4706.

25 Kim, E.K., Kim, H.J., Kim, M.J. *et al.* (2009) How to combine ultrasound and cytological information in decision making about thyroid nodules. *European Radiology*, **19**, 1432–1084.

26 Shin, J.H., Han, B.K., Ko, K. *et al.* (2006) Value of repeat ultrasound-guided fine-needle aspiration in nodules with benign cytological diagnosis. *Acta Radiologica*, **47**, 469–473.

27 Maia, F.F., Matos, P.S., Pavin, E.J. *et al.* (2011) Value of ultrasound and cytological classification system to predict the malignancy of thyroid nodules with indeterminate cytology. *Endocrine Pathology*, **22**, 66–73.

28 Kwak, J.Y., Kim, E.K., Kim, H.J. *et al.* (2009) How to combine ultrasound and cytological information in decision making about thyroid nodules. *European Radiology*, **19**, 1923–1931.

29 Mancuso, A.A. (2005) Oh #*$%#! Another pesky incidental thyroid nodule. *American Journal of Neuroradiology*, **26**, 2444–2445.

30 Hoang, J.K., Raduazo, P., Yousem, D.M. *et al.* (2012) What to do with incidental thyroid nodules on imaging? An approach for the radiologist. *Seminars in Ultrasound, CT and MR*, **33**, 150–157.

31 Shetty, S.K., Maher, M.M., Hahn, P.F. *et al.* (2007) Significance of incidental thyroid lesions detected on CT: correlation among CT, sonography and pathology. *American Journal of Roentgenology*, **188**, 1349–1356.

32 Soelberg, K.K., Bonnema, S.J., Brix, T. *et al.* (2012) Risk of malignancy in thyroid incidentalomas detected by 18F-fluorodeoxyglucose positron emission tomography. A systematic review. *Thyroid*, **22**, 918–925.

33 Ultrasound Training Recommendations for Medical and Surgical Specialities, 2nd edn. Royal College of Radiologists, 2012. BFCR (12) (17).

34 Byung, M.K., Min, J.K., Kim, E.-K. *et al.* (2008) Sonographic differentiation of thyroid nodules with eggshell calcifications. *Journal of Ultrasound in Medicine: Official Journal of the American Institute of Ultrasound in Medicine*, **27**, 1425–1430.

35 Kim, B.K., Choi, Y.S., Kwon, H.J. *et al.* (2013) Relationships between patterns of calcification in thyroid nodules and histopathologic findings. *Endocrine Journal*, **60**, 155–160.

36 Lingam, R.K., Qarib, M.H. & Tolley, N.S. (2013) Evaluating thyroid nodules: predicting and selecting malignant nodules for fine-needle aspiration (FNA) cytology. *Insights into Imaging*, **4**, 617–624.

CHAPTER 5

5 Fine-needle aspiration cytology

5.1. Aspiration cytology of thyroid

Fine needle aspiration cytology (FNAC) is a valuable and cost-effective pre-operative investigation for thyroid nodules in adults.[1–3] The results can reassure that a nodule is benign, triage patients for diagnostic surgery, or provide a definite diagnosis of some thyroid malignancies enabling one-stage therapeutic surgery. FNAC does have drawbacks, however, especially the sometimes high rate of inadequate/unsatisfactory samples; the inability to distinguish between non-neoplastic, benign and malignant follicular lesions[1,4,5] and the difficulty in detecting follicular variant of papillary thyroid carcinoma.[6–12]

It is essential that adequate material is obtained for diagnosis and that the microscopy is performed by pathologists experienced in thyroid disease.[13,14] A high quality service requires close co-operation between biomedical/healthcare scientists, pathologists, radiologists/sonographers and clinicians managing the patients so that appropriate procedures are set up, implemented and monitored.[13]

Aspiration should be performed by an appropriately trained individual with expertise and interest in thyroid disease. They should perform sufficient aspirates to maintain expertise and they should audit their results.[15]

FNAC samples taken with ultrasound (US) guidance (Chapter 4), have increased accuracy[13,16–18] and reduced rates of unsatisfactory samples.[19–22]

Immediate assessment of the sample for adequacy by biomedical scientists or pathologists at the time of aspiration can reduce the rate of unsatisfactory samples and be cost-effective especially if the underlying adequacy rate is low,[23–27] and facilitate collection of material for ancillary tests.

FNAC can also be used in the diagnosis of suspicious lymph nodes and the measurement of thyroglobulin in the washout can improve diagnostic accuracy (Appendix 1).[28,29]

Molecular analysis (e.g. *BRAF* V600E mutation for PTC, alone or part of a panel) is an emerging field and may refine the prediction of both benignity and malignancy in thyroid cytology samples.[30–51]

i All FNAC requests should include full clinical details including a description of the abnormality (diagrams are helpful).
Good Practice Point ☑

ii Tumours may be cystic.[15,52] When cysts are aspirated, all the material aspirated (not just a sample) should be sent to the laboratory without fixation (and therefore without delay). Any suspicious residual mass should be immediately re-aspirated and the specimens identified separately **(2−, D).**

iii A nominated pathologist should be a core member of the local thyroid cancer Multidisciplinary Team (MDT).[53]
National Cancer Peer Review Programme, measure 11-2I-114

iv Thyroid cytology should be reported by a cytopathologist with experience in such samples and with access to colleagues with additional experience for second opinions when appropriate. Such review increases accuracy of cytology[13,54,55] **(2+, C).**
Key recommendation

v There should be routine correlation between the cytological diagnosis and any subsequent histology.
Good Practice Point ☑

vi The cytology report should contain a descriptive section interpreting the findings, followed by the Thy numerical category as defined by RCPath (Section 5.2).
Good Practice Point ☑
Key recommendation

vii Numerical categories increase accuracy,[56] aid local audit, allow comparison with other centres including internationally, and can guide discussion on further management but are not a replacement for the descriptive interpretation. The clinical scenario should be taken into account when reporting the cytology.[1]
Good Practice Point ☑

viii All cases with malignancy on cytology (Thy5), or suspected on cytological (Thy4), clinical or radiological grounds, must be discussed at the MDT meeting.[57]

ix Additional cases (e.g. Thy3 category cytology) can benefit from MDT discussion and this should be at the discretion of the local MDT.
Good Practice Point ☑

x An FNAC which initially yields benign cytology (Thy2) should be repeated if there is any clinical suspicion of malignancy and/or when the US is indeterminate or suspicious[58–62] **(2++, B).**

xi When there is clinical suspicion of malignancy and/or indeterminate or suspicious US features, and an unsatisfactory FNAC (Thy1) is obtained, repeat FNAC is mandatory[63–65] **(2++, B).**

xii When there is discordance between level of clinical suspicion, FNAC or US appearances, management should be discussed in the MDT **(4, C).**

xiii In selected cases and in an MDT context, molecular testing of FNAC material may be helpful in deciding whether diagnostic or therapeutic surgery should be undertaken. Validation, verification and rigorous quality control by laboratories undertaking these tests are essential **(4, D).**

5.2. Diagnostic categories

As noted above (Section 5.1), the Thy numerical diagnostic categories should be used in addition to a full text report. The

Royal College of Pathologists publication should be followed for the terminology, and is summarised below. For full explanation of the categories, see the original RCPath document and any subsequent revision.[66] These UK categories now map exactly to the Bethesda categories used in the USA[67], which facilitates comparison between the two systems.

Thy1 – non-diagnostic. This will include samples reflecting poor operator or preparation technique such as insufficient epithelial cells (the target is 6 groups each of at least 10 well-visualised follicular epithelial cells) or only poorly preserved cells, as well as those reflecting the lesion such as cysts. The suffix Thy1c is used for cyst fluid samples with insufficient colloid and epithelial cells.

Thy2 – non-neoplastic. These samples are adequately cellular and suggest a non-neoplastic lesion such as normal thyroid tissue, a colloid nodule or thyroiditis. Cyst samples containing abundant colloid, even if less that the target number of epithelial cells, can be categorised as Thy2c.

Thy3 – neoplasm possible. This is subdivided into:

Thy3a – when there are atypical features present but not enough to place into any of the other categories. The cytological interpretation should be clearly stated in the report and may include situations such as inability to exclude a follicular neoplasm or papillary carcinoma. Many Thy3a cases reflect suboptimal specimens and can be re-allocated on repeat cytology.

Thy3f – when a follicular neoplasm is suspected. The histological possibilities then include a hyperplastic nodule, follicular adenoma or follicular carcinoma. These cannot be distinguished on cytology alone and a histology sample (e.g. diagnostic hemithyroidectomy) will be required for diagnosis. Follicular variant of papillary thyroid carcinoma will also sometimes fall into this category when the nuclear features are more subtle.

Thy4 – suspicious of malignancy but definite diagnosis of malignancy is not possible. The type of malignancy suspected should be stated in the report and is usually papillary carcinoma.

Thy5 – diagnostic of malignancy. The type of malignancy should be stated, for example papillary, medullary or anaplastic thyroid carcinoma, lymphoma, or metastatic disease.

The likelihood of a malignancy on subsequent histology increases with increasing Thy category and should be 100% for Thy5, though rates of 98–99% are reported.[68,69]

Suspicious cytology (Thy4) is associated with malignant histology in about 68–70%.[69,70]

Follicular or indeterminate cytology (Thy3) is followed by malignant histology in around 9·5–43% of cases[9,69–77] the risk being highest with suspicious ultrasound features.[75]

There is a false negative rate for benign (Thy2) cytology results (usually <3%).[62] Malignancy can be found in nodules with Thy1 cytology (4·5–8·5%[22,63]), especially if the lesion is cystic (14·3%).[89]

The likely clinical action is not usually documented within the cytology report. The following clinical action is usually anticipated by the cytopathologist while reporting the FNA (Fig. 4.1):

Thy1 – ultrasound assessment ± repeat FNAC.
Thy2 – correlate with clinical and radiological (US) findings.
Thy3a – further investigation, usually US assessment ± repeat FNAC (Thy3a FNAC on repeat sample requires MDT discussion).
Thy3f – diagnostic hemithyroidectomy.
Thy4 – diagnostic hemithyroidectomy.
Thy5 – therapy appropriate to tumour type, usually surgery for papillary or medullary thyroid carcinomas.

There is interobserver variation in the interpretation of follicular-patterned lesions in both cytology and histology.[69,78–80] Subdivision of indeterminate cytology (Thy3) further stratifies the risk of malignancy.[8,65,81–86] Immunocytochemical and molecular methods may also assist in stratification of risk.[87–91]

References

1 Bajaj, Y., De, M. & Thompson, A. (2006) Fine needle aspiration cytology in diagnosis and management of thyroid disease. *Journal of Laryngology and Otology*, **120**, 467–469.
2 Altincik, A., Demir, K., Abaci, A. *et al.* (2010) Fine-needle aspiration biopsy in the diagnosis and follow-up of thyroid nodules in childhood. *Journal of Clinical Research in Pediatric Endocrinology*, **2**, 78–80.
3 Raina, B., Misri, A., Kanotra, J.P. *et al.* (2011) Profile of fine needle aspiration cytology of thyroid nodule and its histopathological correlation. *JK Practitioner*, **16**, 87–91.
4 Pauzar, B., Staklenac, B. & Loncar, B. (2010) Fine needle aspiration biopsy of follicular thyroid tumours. *Collegium Antropologicum*, **34**, 87–91.
5 Schreiner, A.M. & Yang, G.C.H. (2012) Adenomatoid nodules are the main cause for discrepant histology in 234 thyroid fine-needle aspirates reported as follicular neoplasm. *Diagnostic Cytopathology*, **40**, 375–379.
6 Aron, M., Mallik, A. & Verma, K. (2006) Fine needle aspiration cytology of follicular variant of papillary carcinoma of the thyroid: morphologic pointers to its diagnosis. *Acta Cytologica*, **50**, 663–668.
7 Chang, H.Y., Lin, J.D., Chou, S.C. *et al.* (2006) Clinical presentations and outcomes of surgical treatment of follicular variant of the papillary thyroid carcinomas. *Japanese Journal of Clinical Oncology*, **36**, 688–693.
8 Sangalli, G., Serio, G., Zampatti, C. *et al.* (2006) Fine needle aspiration cytology of the thyroid: a comparison of 5469 cytological and final histological diagnoses. *Cytopathology*, **17**, 245–250.
9 Rago, T., Di Coscio, G., Basolo, F. *et al.* (2007) Combined clinical, thyroid ultrasound and cytological features help to predict thyroid malignancy in follicular and Hurthle cell thyroid lesions: results from a series of 505 consecutive patients. *Clinical Endocrinology*, **66**, 13–20.
10 Proietti, A., Giannini, R., Ugolini, C. *et al.* (2010) BRAF status of follicular variant of papillary thyroid carcinoma and its relationship to its clinical and cytological features. *Thyroid*, **20**, 1263–1270.
11 Kurian, E.M., Dawlett, M., Wang, J. *et al.* (2012) The triage efficacy of fine needle aspiration biopsy for follicular variant of pap-

illary thyroid carcinoma using the Bethesda reporting guidelines. *Diagnostic Cytopathology*, **40**(supp 1), E69–E73.
12 Yang, G., Fried, K., Yakoushina, T.V. *et al.* (2013) Encapsulated follicular variant of papillary thyroid carcinoma: fine-needle aspiration with ultrasound and histologic correlation of 41 cases. *Acta Cytologica*, **57**, 26–32.
13 Porterfield, J.R. Jr, Grant, C.S., Dean, D.S. *et al.* (2008) Reliability of benign fine needle aspiration cytology of large thyroid nodules. *Surgery*, **144**, 963–968.
14 Alam, M., Qureshi, H. & Jan, Q.A. (2010) Accuracy of FNAC as a diagnostic modality in the management of solitary thyroid nodule. *Journal of Medical Sciences*, **18**, 94–96.
15 Choi, S.H., Han, K.H., Yoon, J.H. *et al.* (2011) Factors affecting inadequate sampling of ultrasound-guided fine-needle aspiration biopsy of thyroid nodules. *Clinical Endocrinology*, **74**, 776–782.
16 Izquierdo, R., Arekat, M.R., Knudson, P.E. *et al.* (2006) Comparison of palpation-guided versus ultrasound-guided fine-needle aspiration biopsies of thyroid nodules in an outpatient endocrinology practice. *Endocrine Practice*, **12**, 609–614.
17 Nixon, I.J., Ganly, I., Hann, L.E. *et al.* (2010) Nomogram for predicting malignancy in thyroid nodules using clinical, biochemical, ultrasonographic, and cytologic features. *Surgery*, **148**, 1120–1127.
18 Gonzalez-Gonzalez, A., Mate-Valdezate, A., Parra-Arroyo, A. *et al.* (2011) New guidelines for the management of thyroid nodules and differentiated thyroid cancer. *Minerva Endocrinologica*, **36**, 7–12.
19 Cai, X.J., Valiyaparambath, N., Nixon, P. *et al.* (2006) Ultrasound guided fine needle aspiration cytology in the diagnosis and management of thyroid nodules. *Cytopathology*, **17**, 251–256.
20 Cesur, M., Corapcioglu, D., Bulut, S. *et al.* (2006) Comparison of palpation-guided fine-needle aspiration biopsy to ultrasound-guided fine-needle aspiration biopsy in the evaluation of thyroid nodules. *Thyroid*, **16**, 555–561.
21 Chen, P.-Y., Chiou, S.-C., Yeh, H.-Y. *et al.* (2010) Correlation of ultrasonography with fine needle aspiration cytology and final pathological diagnoses in patients with thyroid nodules. *Chinese Journal of Radiology*, **35**, 1–7.
22 Al Maqbali, T., Tedla, M., Weickert, M.O. *et al.* (2012) Malignancy risk analysis in patients with inadequate fine needle aspiration cytology (FNAC) of the thyroid. *PLoS One*, **7**, e49078.
23 Breeze, J., Poller, D.N., Gibson, D. *et al.* (2013) Rapid on-site assessment of specimens by biomedical scientists improves the quality of head and neck fine needle aspiration cytology. *Cytopathology*. doi: 10.1111/cyt.12106 [Epub ahead of print].
24 Poller, D.N. & Kandaswamy, P. (2013) A simplified economic approach to thyroid FNA cytology and surgical intervention in thyroid nodules. *Journal of Clinical Pathology*, **66**, 583–588.
25 Simsel, G.G., Ertugrul, D.T., Guresci, S. *et al.* (2013) Is there a role for on-site evaluation of thyroid fine needle aspiration to reduce the nondiagnostic rate? *Endocrine Pathology*, **24**, 57–61.
26 Witt, B.L. & Schmidt, R.L. (2013) Rapid onsite evaluation improves the adequacy of fine-needle aspiration for thyroid lesions: a systematic review and meta-analysis. *Thyroid*, **23**, 428–435.
27 Zanocco, K., Pitelka-Zengou, L., Dalal, S. *et al.* (2013) Routine on-site evaluation of specimen adequacy during initial ultrasound-guided fine needle aspiration of thyroid nodules: a cost-effectiveness analysis. *Annals of Surgical Oncology*, **20**, 2462–2467.
28 Giovanella, L., Bongiovanni, M. & Trimboli, P. (2013) Diagnostic value of thyroglobulin assay in cervical lymph node fine-needle aspirations for metastatic differentiated thyroid cancer. *Current Opinion in Oncology*, **25**, 6–13.
29 Chung, J., Kim, E.K., Lim, H. *et al.* (2014) Optimal indication of thyroglobulin measurement in fine-needle aspiration for detecting lateral metastatic lymph nodes in patients with papillary thyroid carcinoma. *Head and Neck*, **36**, 795–801.
30 Chung, K.W., Yang, S.K., Lee, G.K. *et al.* (2006) Function of BRAFV600E mutation on fine needle aspiration specimens of thyroid nodule refines cyto-pathology diagnosis, especially in BRAF600E mutation-prevalent area. *Clinical Endocrinology*, **65**, 660–666.
31 Rowe, L.R., Bentz, B.G. & Bentz, J.S. (2006) Utility of BRAF V600E mutation detection in cytologically indeterminate thyroid nodules. *CytoJournal*, **3**, 10.
32 Sapio, M.R., Posca, D., Troncone, G. *et al.* (2006) Detection of BRAF mutation in thyroid papillary carcinomas by mutant allele-specific PCR amplification(MASA). *European Journal of Endocrinology*, **154**, 341–348.
33 Kumagai, A., Namba, H., Akanov, Z. *et al.* (2007) Clinical implications of pre-operative rapid BRAF analysis for papillary thyroid cancer. *Endocrine Journal*, **54**, 399–405.
34 Bentz, B.G., Miller, B.T., Holden, J.A. *et al.* (2009) B-RAF V6000E mutational analysis of fine needle aspirates correlates with diagnosis of thyroid nodules. *Otolaryngology – Head and Neck Surgery*, **140**, 709–714.
35 Xing, M., Clark, D., Guan, H. *et al.* (2009) BRAF mutation testing of thyroid fine-needle aspiration biopsy specimens for preoperative risk stratification in papillary thyroid cancer. *Journal of Clinical Oncology*, **27**, 2977–2982.
36 Yip, L., Nikforova, M.N., Carty, S.E. *et al.* (2009) Optimising surgical treatment of papillary thyroid carcinoma associated with BRAF mutation. *Surgery*, **146**, 1215–1223.
37 Cantara, S., Capezzone, M., Marchisotta, S. *et al.* (2010) Impact of proto-oncogene mutation detection in cytological specimens from thyroid nodules improves the diagnostic accuracy of cytology. *Journal of Clinical Endocrinology and Metabolism*, **95**, 1365–1369.
38 Kim, S.W., Lee, J.I., Kim, J.W. *et al.* (2010) BRAFV600E mutation analysis in fine needle aspiration cytology specimens for evaluation of thyroid nodule: a large series in a BRAFV600E-prevalent population. *Journal of Clinical Endocrinology and Metabolism*, **95**, 3693–3700.
39 Lee, H.J., Choi, J., Hwang, T.S. *et al.* (2010) Detection of BRAF mutations in thyroid nodules by allele-specific PCR using a dual priming oligonucleotide system. *American Journal of Clinical Pathology*, **133**, 802–808.
40 Moses, W., Weng, J., Sansano, I. *et al.* (2010) Molecular testing for somatic mutations improves the accuracy of thyroid fine-needle aspiration biopsy. *World Journal of Surgery*, **34**, 2589–2594.
41 Ferraz, C., Eszlinger, M. & Paschke, R. (2011) Current state and future perspective of molecular diagnosis of fine-needle aspiration biopsy of thyroid nodules. *Journal of Clinical Endocrinology and Metabolism*, **96**, 2016–2026.
42 Filicori, F., Keutgen, X.M., Buitrago, D. *et al.* (2011) Risk stratification of indeterminate thyroid fine-needle aspiration biopsy specimens based on mutation analysis. *Surgery*, **150**, 1085–1091.
43 Li, H., Robinson, K.A., Anton, B. *et al.* (2011) Cost-effectiveness of a novel molecular test for cytologically indeterminate thyroid nodules. *Journal of Clinical Endocrinology and Metabolism*, **96**, E1719–E1726.

44 Moon, H.J., Kim, E.K., Chung, W.Y. *et al.* (2011) Diagnostic value of BRAF(V600E) mutation analysis of thyroid nodules according to ultrasonographic features and the time of aspiration. *Annals of Surgical Oncology*, **18**, 792–799.

45 Nikiforov, Y.E., Ohori, N.P., Hodak, S.P. *et al.* (2011) Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. *Journal of Clinical Endocrinology and Metabolism*, **96**, 3390–3397.

46 Yeo, M.K., Liang, Z.L., Oh, T. *et al.* (2011) Pyrosequencing cut-off value identifying BRAFV600E mutation in fine needle aspiration samples of thyroid nodules. *Clinical Endocrinology*, **75**, 555–560.

47 Canadas-Garre, M., Becerra-Massare, P., Lopez de la Torre-Casares, M. *et al.* (2012) Reduction of false-negative papillary thyroid carcinomas by the routine analysis of BRAF(T1799A) mutation on fine-needle aspiration biopsy specimens: a prospective study of 814 thyroid FNAB patients. *Annals of Surgery*, **255**, 986–992.

48 Marchetti, I., Iervasi, G., Mazzanti, C.M. *et al.* (2012) Detection of the BRAFV600E mutation in fine needle aspiration cytology of thyroid papillary microcarcinoma cells selected by manual macrodissection: an easy tool to improve the preoperative diagnosis. *Thyroid*, **22**, 292–298.

49 Monaco, S.E., Pantanowitz, L., Khalbuss, W.E. *et al.* (2012) Cytomorphological and molecular genetic findings in pediatric thyroid fine needle aspiration. *Cancer Cytopathology*, **120**, 342–350.

50 Moon, W.J., Choi, N., Choi, J.W. *et al.* (2012) BRAF mutation analysis and sonography as adjuncts to fine-needle aspiration cytology of papillary thyroid carcinoma: their relationships and roles. *American Journal of Roentgenology*, **198**, 668–674.

51 Park, J.Y., Kim, W.Y., Hwang, T.S. *et al.* (2013) BRAF and RAS mutations in follicular variants of papillary thyroid carcinoma. *Endocrine Pathology*, **24**, 69–76.

52 Yang, G.C., Stern, C.M. & Messina, A.V. (2010) Cystic papillary thyroid carcinoma in fine needle aspiration may represent a subset of the encapsulated variant in WHO classification. *Diagnostic Cytopathology*, **38**, 721–726.

53 National Cancer Peer Review – National Cancer Action Team. Manual for Cancer Services: Head and Neck Measures Version 3.0. http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CDEQFjAA&url=http%3A%2F%2Fwww.cquins.nhs.uk%2Fdownload.php%3Fd%3Dresources%2Fmeasures%2FHeadNeck_April2013.pdf&ei=ycCZUqLaNcarhAeX5YCoCA&usg=AFQjCNG64LiorBQOs2QpPgTu6lYlz6Ne_w&bvm=bv.57155469,d.ZG4.

54 Tan, Y.Y., Kebebew, E., Reiff, E. *et al.* (2007) Does routine consultation of thyroid fine-needle aspiration cytology change surgical management? *Journal of the American College of Surgeons*, **205**, 8–12.

55 Davidov, T., Trooskin, S.Z., Shanker, B.-A. *et al.* (2010) Routine second-opinion cytopathology review of thyroid fine needle aspiration biopsies reduces diagnostic thyroidectomy. *Surgery*, **148**, 1294–1299.

56 Rabaglia, J.L., Kabbani, W., Wallace, L. *et al.* (2010) Effect of the Bethesda system for reporting thyroid cytopathology on thyroidectomy rates and malignancy risk in cytologically indeterminate lesions. *Surgery*, **148**, 1267–1272.

57 Improving outcomes in Head and Neck Cancer. http://www.nice.org.uk/nicemedia/live/10897/28851/28851.pdf.

58 Hambly, N.M., Gonen, M. & Gerst, S.R. (2011) Implementation of Evidence-based guidelines for thyroid nodule biopsy: a model for establishment of practice standards. *American Journal of Roentgenology*, **196**, 655–660.

59 Kim, M.J., Kim, E.-K. & Park, S. (2008) US-guided fine-needle aspiration of thyroid nodules: indications, techniques and results. *Radiographics*, **28**, 1869–1889.

60 Ahn, S.S., Kim, E.-K. & Kang, D.R. (2010) Biopsy of thyroid nodules: comparison of three sets of guidelines. *American Journal of Roentgenology*, **194**, 31–37.

61 Kwak, J.Y., Koo, H. & Youk, J.H. (2010) Value of US correlation of a thyroid nodule with initially benign cytologic results. *Radiology*, **254**, 292–300.

62 Kwak, J.Y., Kim, E.K., Kim, H.J. *et al.* (2009) How to combine ultrasound and cytological information in decision making about thyroid nodules. *European Radiology*, **19**, 1923–1931.

63 Orija, I.B., Pineyro, M., Biscotti, C. *et al.* (2007) Value of repeating a nondiagnostic thyroid fine-needle aspiration biopsy. *Endocrine Practice*, **13**, 735–742.

64 Yoon, J.H., Moon, H.J., Kim, E.K. *et al.* (2011) Inadequate cytology in thyroid nodules: should we repeat aspiration or follow-up? *Annals of Surgical Oncology*, **18**, 1282–1289.

65 Olson, M.T., Clark, D.P., Erozan, Y.S. *et al.* (2011) Spectrum of risk of malignancy in subcategories of 'atypia of undetermined significance'. *Acta Cytologica*, **55**, 518–525.

66 The Royal College of Pathologists (2009) Guidance on the Reporting of Thyroid Cytology Specimens. London. www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/g089guidanceonthereportingofthyroidcytologyfinal.pdf.

67 The Bethesda System for Reporting (2010) Thyroid Cytopathology: Definitions, Criteria and Explanatory Notes by Syed Z. Ali and Edmund S. Cibas. Springer.

68 Jo, V.Y., Stelow, E.B., Dustin, S.M. *et al.* (2010) Malignancy risk for fine-needle aspiration of thyroid lesions according to the Bethesda System for reporting thyroid cytopathology. *American Journal of Clinical Pathology*, **134**, 450–456.

69 Wang, C.C., Friedman, L., Kennedy, G.C. *et al.* (2011) A large multicentre correlation study of thyroid nodule cytopathology and histopathology. *Thyroid*, **21**, 243–251.

70 Wu, H.H.-J., Jones, J.N. & Osman, J. (2006) Fine-needle aspiration cytology of the thyroid: ten years experience in a community teaching hospital. *Diagnostic Cytopathology*, **34**, 93–96.

71 Gulcelik, N.E., Gulcelik, M.A. & Kuru, B. (2008) Risk of malignancy in patients with follicular neoplasm: predictive value of clinical and ultrasonographic features. *Archives of Otolaryngology – Head and Neck Surgery*, **134**, 1312–1315.

72 Sorrenti, S., Trimboli, P., Catania, A. *et al.* (2009) Comparison of malignancy rate in thyroid nodules with cytology of indeterminate follicular or indeterminate hurthle cell neoplasm. *Thyroid*, **19**, 355–360.

73 Chen, S.J., Chang, C.Y., Chang, K.Y. *et al.* (2010) Classification of the thyroid nodules based on characteristic sonographic textural feature and correlated histopathology using hierarchical support vector machines. *Ultrasound in Medicine and Biology*, **36**, 2018–2026.

74 Broome, J.T. & Solorzano, C.C. (2011) The impact of atypia/follicular lesion of undetermined significance on the rate of malignancy in thyroid fine-needle aspiration: evaluation of the Bethesda System for Reporting Thyroid Cytopathology. *Surgery*, **150**, 1234–1241.

75 Maia, F.F., Matos, P.S., Pavin, E.J. *et al.* (2011) Value of ultrasound and cytological classification system to predict the malignancy of thyroid nodules with indeterminate cytology. *Endocrine Pathology*, **22**, 66–73.

76 Roh, M.H., Jo, V.Y., Stelow, E.B. *et al.* (2011) The predictive value of the fine-needle aspiration diagnosis 'suspicious for a follicular neoplasm, hurthle cell type' in patients with hashimoto thyroiditis. *American Journal of Clinical Pathology*, **135**, 139–145.

77 VanderLaan, P.A., Marqusee, E. & Krane, J.F. (2011) Clinical outcome for atypia of undetermined significance in thyroid fine-needle aspirations: should repeated fna be the preferred initial approach? *American Journal of Clinical Pathology*, **135**, 770–775.

78 Elsheikh, T.M., Asa, S.L., Chan, J.K. *et al.* (2008) Interobserver and intraobserver variation among experts in the diagnosis of thyroid follicular lesions with borderline nuclear features of papillary carcinoma. *American Journal of Clinical Pathology*, **130**, 736–744.

79 Kocjan, G., Chandra, A., Cross, P.A. *et al.* (2011) The interobserver reproducibility of thyroid fine-needle aspiration using the UK Royal College of Pathologists' classification system. *American Journal of Clinical Pathology*, **135**, 852–859.

80 Duggal, R., Rajwanshi, A., Gupta, N. *et al.* (2011) Interobserver variability amongst cytopathologists and histopathologists in the diagnosis of neoplastic follicular patterned lesions of thyroid. *Diagnostic Cytopathology*, **39**, 235–241.

81 Sahin, M., Gursoy, A., Tutuncu, N.B. *et al.* (2006) Prevalence and prediction of malignancy in cytologically indeterminate thyroid nodules. *Clinical Endocrinology*, **65**, 514–518.

82 Tysome, J.R., Chandra, A., Chang, F. *et al.* (2009) Improving prediction of malignancy of cytologically indeterminate thyroid nodules. *British Journal of Surgery*, **96**, 1400–1405.

83 Williams, M.D., Suliburk, J.W., Staerkel, G.A. *et al.* (2009) Clinical significance of distinguishing between follicular lesion and follicular neoplasm in thyroid fine-needle aspiration biopsy. *Annals of Surgical Oncology*, **16**, 3146–3153.

84 Lakhani, R., Rourke, T., Jefferis, A. *et al.* (2011) Thy3 cytology: what to do next? *Annals of the Royal College of Surgeons of England*, **93**, 225–228.

85 Turanli, S., Pirhan, Y., Ozcelik, C.K. *et al.* (2011) Predictors of malignancy in patients with a thyroid nodule that contains Hurthle cells. *Otolaryngology – Head and Neck Surgery*, **144**, 514–517.

86 Bongiovanni, M., Triponez, F., McKee, T.A. *et al.* (2009) Fine-needle aspiration of the diffuse sclerosing variant of papillary thyroid carcinoma masked by florid lymphocytic thyroiditis; a potential pitfall: a case report and review of the literature. *Diagnostic Cytopathology*, **37**, 671–675.

87 Bartolazzi, A., Orlandi, F., Saggiorato, E. *et al.* (2008) Galectin-3-expression analysis in the surgical selection of follicular thyroid nodules with indeterminate fine-needle aspiration cytology: a prospective multicentre study. *The Lancet Oncology*, **9**, 543–549.

88 Sofiadis, A., Tani, E., Foukakis, T. *et al.* (2009) Diagnostic and prognostic potential of MIB-1 proliferation index in thyroid fine needle aspiration biopsy. *International Journal of Oncology*, **35**, 369–374.

89 Garcia-Pascual, L., Barahona, M.-J., Balsells, M. *et al.* (2011) Complex thyroid nodules with nondiagnostic fine needle aspiration cytology: histopathologic outcomes and comparison of the cytologic variants (cystic vs. acellular). *Endocrine*, **39**, 33–40.

90 Cochand-Priollet, B., Dahan, H., Laloi-Michelin, M. *et al.* (2011) Immunohistochemistry with cytokeratin 19 and ant-human mesothelial cell antibody (HBME1) incrases the diagnos tic accuracy of thyroid fine-needle aspirations: preliminary report of 150 liquid-based fine-needle aspirations with histological control. *Thyroid*, **21**, 1067–1073.

91 Fadda, G., Rossi, E.D., Raffaelli, M. *et al.* (2011) Follicular thyroid neoplasms can be classified as low- and high-risk according to HBME-1 and Galectin-3 expression on liquid-based fine-needle cytology. *European Journal of Endocrinology*, **165**, 447–453.

CHAPTER 6

6 Primary treatment of differentiated thyroid cancer

6.1. Timescale

i Patients with suspected thyroid cancer should normally be seen in accordance with the national target for urgent referrals (currently 2 weeks) (Chapter 3).
Good Practice Point ☑

ii If there are progressive/severe respiratory problems associated with a thyroid mass, patients must be referred and seen without delay.
Good Practice Point ☑

iii Patients with new onset of stridor and a thyroid mass must be assessed as emergency cases.
Good Practice Point ☑

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, Chapter 3, Fig. 3.1).
Good Practice Point ☑

6.2. Staging and risk assignment

i Patients should be staged using the TNM classification (Table 2.1), and assigned to the appropriate ATA risk group (Table 2.2) (**2+**, **C**).

6.3. Documentation

i The following should be recorded in the medical records:
Good Practice Point ☑

- family history and past medical history;
- date of surgery;
- name of surgeon, assistant and anaesthetist;
- extent of surgery;
- complications of surgery;
- presence or absence of metastases including number and location of lymph nodes;
- Fine-needle aspiration cytology (FNAC), histology and pathologically staged according to TNM (pTNM) staging;
- curative or palliative intent;
- date of RRA/therapy;
- activity of RRA/therapy and side effects;
- post-ablation iodine scan result;
- follow-up arrangements.

CHAPTER 7

7 Surgery for differentiated thyroid cancer

There is a strong case for patients with thyroid cancer to be operated on and treated by clinicians who have appropriate training and experience. Complication rates from thyroid surgery are lower when patients, adult and paediatric, are treated by 'high volume' surgeons.[1–3] Membership of the British Association of Endocrine and Thyroid Surgeons (BAETS) mandates annual returns and provides comparative performance data on surgical numbers and outcome measures (http://baets.e-dendrite.com).

i The surgeon should have *training and expertise in the management of thyroid cancer* and be a core member of the multidisciplinary team (MDT) (Improving outcomes in Head and Neck Cancer http://www.nice.org.uk/nicemedia/live/10897/28851/28851.pdf)
Key recommendation

The Manual of Cancer Services and Current Peer Review standards[4] require that:

i Surgeons who operate on patients with thyroid cancer should perform a minimum of 20 thyroidectomies per year
National Cancer Peer Review Programme, measure 11-2I-149

ii Cervical lymph node dissection should be performed by MDT authorised surgeons
National Cancer Peer Review Programme, measure 11-2I-146

7.1. Terminology

Compliance with appropriate and clear definitions of anatomy and surgical procedures is essential. The terms in Tables 7.1, 7.2 and 7.3 should be used.
Good Practice Point ☑

7.2. Pre-operative imaging

All patients with suspected or diagnosed thyroid cancer should have had a pre-operative ultrasound (US) (Chapter 4). US of the neck alone is sufficient for patients planned for diagnostic thyroid surgery (see section 7.3 below) and allows adequate pre-operative assessment of both extra-thyroidal extension and lateral neck node metastases in most cases. For detailed assessment of the central compartment, mediastinal lymph nodes and lungs, additional cross-sectional imaging by CT may be required.[5–7]

i In patients with thyroid cancer assessment of extra-thyroidal extension and lymph node disease in the central and lateral neck compartments should be undertaken pre-operatively. A combination of ultrasound (US) and computed tomography (CT)/magnetic resonance imaging (MRI) imaging is advised depending upon local expertise.
Good Practice Point ☑
Key recommendation

ii Lymph nodes that are equivocal/suspicious on US, should be assessed by fine needle aspiration cytology (FNAC). Measurement of Tg in aspirate washout fluid may aid the diagnosis of lymph node metastasis (Appendix 1, 1.2) (**4**, **D**).

iii When CT is utilized in pre-operative assessment of thyroid cancer, there should be a 2 month delay between the use of iodinated contrast media and subsequent ^{131}I therapy (see Chapter 9.2) (**4**, **D**).

7.3. Preparation for surgery

i The operating surgeon should obtain consent after full discussion, although this may be delegated to a suitably trained and qualified person as specified in GMC Guidance (2008).[8]
Good Practice Point ☑

ii The specific complications of thyroid surgery/lymph node dissection should be discussed as well as those relevant complications which can occur at any surgical procedure; this discussion should be detailed in the clinical record. Additional written or audio-visual material are recommended (Appendix 4, Patient Information Leaflet 3), but are not a replacement for verbal consent[9] (**4**, **D**).

iii The risk of venous thromboembolism (VTE) is not increased in patients undergoing thyroid cancer surgery.[10,11] In the absence of other risk factors for VTE, routine use of chemoprophylaxis is not required for patients undergoing thyroid surgery. VTE prophylaxis, in the form of graduated compression hose and/or peri-operative calf compression devices should be used in all cases[12] (**1++**, **A**).

iv In patients with suspected or proven thyroid cancer, assessment of vocal cord function is recommended prior to surgery for diagnostic and audit purposes[13] (**2++**, **B**).

7.4. Surgical approach to laryngeal nerves and parathyroid glands

Permanent damage to a recurrent laryngeal nerve should occur in significantly <5% of patients who have undergone surgery for thyroid cancer. Bilateral injuries are extremely rare. In expert centres, nerve injury rates are no higher after re-operative central neck node dissection surgery[14,15] or for recurrent thyroid cancer.[16–19] Infiltration by tumour contributes to recurrent laryngeal nerve palsy rates in malignant disease. Lymph node dissection in the central compartment (level VI) is associated with an increased risk

Table 7.1. Recommended terminology relating to thyroid surgery

The terms below should be used:
(**Good Practice Point**) ☑

Thyroid surgery
- *Hemithyroidectomy:* the complete removal of one thyroid lobe including the isthmus.
- *Near-total lobectomy:* a total lobectomy leaving behind only the smallest amount of thyroid tissue (significantly less than 1 g) to protect the recurrent laryngeal nerves.
- *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.
- *Total thyroidectomy:* the removal of both thyroid lobes, isthmus and pyramidal lobe.

i 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 (**4**, **D**).

of temporary but not permanent hypoparathyroidism compared with total thyroidectomy alone.[20]

i The recurrent laryngeal nerve/s should be identified in virtually all patients and when preoperative laryngoscopy has indicated normal vocal cord function, preserved (**4**, **D**).

ii Attempts should be made to identify/protect preserve the external branch of the superior laryngeal nerves[13] by ligation of the superior thyroid vessels at the capsule of the gland. External laryngeal nerve injury has an associated morbidity, particularly in voice-quality changes. Injury rates may be higher than for recurrent laryngeal nerve damage[21] (**1−**, **B**).

iii Parathyroid glands should whenever possible be identified and preserved. If their vascular supply is compromised, the gland/s should be excised and re-implanted into muscle (**4**, **D**).

7.5. Diagnostic thyroid surgery

For patients with Thy3 fine-needle aspiration cytology (FNAC) who require diagnostic surgery (Chapter 5.2), hemithyroidectomy (Table 7.1) is appropriate. For patients with Thy4 FNAC, from a small, well defined target lesion suspicious of papillary (or medullary thyroid) cancer a diagnostic hemithyroidectomy/lymph node biopsy and positive intra-operative frozen section facilitates single stage therapeutic surgery.[22] Frozen section is not appropriate for follicular lesions.

A total thyroidectomy may be appropriate for patients with a Thy3/Thy4 cytology, if there is an associated symptomatic thyroid disorder (e.g. multinodular goitre/Graves' disease).

i For patients with Thy3f or Thy4 FNAC a diagnostic hemithyroidectomy is recommended (**3**, **D**).

Key recommendation

ii For patients with Thy3a FNAC who require surgery a diagnostic hemithyroidectomy is recommended (**3**, **D**).

iii In circumstances when there are additional indications for thyroidectomy, therapeutic surgery for Thy3f or Thy4 FNAC may be justified if supported by the MDT (**4**, **D**).

7.6. Therapeutic surgery for thyroid cancer

Thyroid surgery for papillary thyroid carcinoma. Surgery for papillary microcarcinoma (microPTC) is discussed in Chapter 8.

The management of patients with pT4b disease is described in section 7.8 below.

Total thyroidectomy for large tumours or tumours of any size with additional risk tactors has been shown to be associated with fewer recurrences and better survival.[23,24] For patients with tumours 4 cm or smaller and no risk factors, hemithyroidectomy without radioiodine remnant ablation (RRA) is reported to have an equally favourable outcome to total thyroidectomy, though all studies are retrospective.[25–30] This could apply to non-invasive encapsulated (or partly encapsulated) follicular variant papillary thyroid cancer (FVPTC).[31]

Table 7.2. Recommended terminology relating to lymph nodes

The terms listed below for lymph node groups and surgery should be used
Good Practice Point ☑

Lateral compartment of neck[62]

Level I Submental and submandibular nodes

Level II Deep cervical chain nodes from the skull base to the level of the hyoid, which are further divided by their relationship to the accessory nerve: IIa (medial) and IIb (lateral)

Level III Deep cervical chain nodes from the level of the hyoid to the level of the cricoid cartilage

Level IV Deep cervical chain nodes from the level of the cricoid to the level of the clavicle

Level V Posterior triangle nodes (anterior border is posterior border of sternomastoid, posterior border is anterior border of trapezius) subdivided into Va and Vb. The American Thyroid Association (ATA) Consensus Review on lateral neck dissection defines levels Va (above) and Vb (below) as separated by a plane from the inferior border of the cricoid cartilage[62]

Central compartment of neck[90]

Level VI and VII Prelaryngeal, pretracheal and paratracheal nodes from the hyoid bone superiorly to the level of the innominate artery inferiorly and to the carotid arteries laterally

Compartment 4[91]

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

Table 7.3. Recommended terminology relating to lymph node surgery

The terms listed below should be used
Good Practice Point ☑

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: radical neck dissection removes all 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)
MRND involves removal of lymph nodes in levels I–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.

Patients with 'radiation-induced' thyroid cancer appear to present with more advanced disease,[32,33] but there is conflicting evidence as to whether outcome or cause specific survival is worse[33] or no different[34–36] from patients without prior irradiation

i Total thyroidectomy is recommended for patients with tumours greater than 4 cm in diameter, or tumours of any size in association with any of the following characteristics: multifocal disease, bilateral disease, extra-thyroidal spread (pT3 and pT4a), familial disease, and those with clinically or radiologically involved nodes and/or distant metastases (**2−**, **D**).

Key recommendation

ii In patients with radiation induced tumours >1–≤4 cm in diameter and no other risk factors, **Personalised Decision Making** is recommended (Chapter 2.4, and Table 2.4) (**4**, **D**).

iii The evidence for an advantage of total thyroidectomy compared to hemithyroidectomy[27,37] in patients with unifocal tumours >1–≤4 cm in diameter, age <45 years, with no extra-thyroidal spread, no familial disease, no evidence of lymph node involvement, no angioinvasion and no distant metastases, is unclear. In such cases **Personalised Decision Making** is recommended (Chapter 2.4, and Table 2.4) (**4**, **D**).

Lymph node surgery in papillary thyroid cancer. Prophylactic central compartment lymph node dissection—Analysis of cases from the Surveillance, Epidemiology, and End Results (SEER) database indicate that lymph node metastasis is associated with increased risk of death[38,39] particularly in patients aged > 45 years. The benefit of prophylactic central compartment node surgery in terms of improved disease-specific survival[40] or recurrence-free survival is not proven.[41–44]

Protagonists of prophylactic central compartment lymph node dissection (PCCND) report the benefit of accurate staging[45,46] and its impact on the use/activity of radioiodine, reduced post-treatment basal/stimulated thyroglobulin (sTg) concentrations and reduction in loco-regional recurrence. Although PCCND is associated with lower pre-ablation Tg concentrations and a higher rate of undetectable Tg, it is reported that the differences are not apparent at 6 months post-treatment[45,47]

- It is variously estimated that 20–31 PCCND are required to prevent one re-operation/local recurrence.[48,49]
- The relative risk of loco-regional recurrence in pN_1 patients with clinically uninvolved lymph nodes (cN_0) is low (2%, and 4% in patients with < 5 lymph node metastases).[50]

These studies highlight the controversy regarding the appropriateness of PCCND in patients with clinically or radiologically N_0 PTC. The potential benefits of prophylactic surgery should also be judged in the context of potential for increased morbidity associated with the injury to the recurrent laryngeal nerves and parathyroid glands.

A systematic review and meta analysis[20] has compared short term (<5 years) loco-regional recurrence and surgical complications in patients undergoing total thyroidectomy alone with those treated by total thyroidectomy and PCCND. The review identifies a possible 35% reduction in the risk of loco-regional recurrence in patients treated with prophylactic node surgery but the impact of increased use of radioiodine remnant ablation (RRA) and selection bias on this reduction in risk is unclear. Another meta analysis failed to identify significant differences in the rates of loco-regional recurrence or of permanent complications in patients undergoing PCCND for PTC compared to patients undergoing total thyroidectomy alone.[49]

Male gender has previously been considered as an additional risk factor for reduced disease-specific survival, but two recent studies have failed to confirm that it is an independent risk factor for survival.[51,52] There is uncertainty as to whether a sole finding of microscopic extra-thyroidal extension (pT3) is an adverse risk factor.[53,54] It is unclear therefore whether gender and microscopic extra-thyroidal extension can be used in decision making about PCCND.

i Central compartment neck dissection is not recommended for patients without clinical or radiological evidence of lymph node involvement, who have all of the following characteristics: classical type PTC, <45 years, unifocal tumour, ≤4 cm, no extra-thyroidal extension on US (**1−**, **C**).

Key recommendation

ii The evidence for an advantage of PCCND compared to no PCCND in patients with clinically/radiologically uninvolved neck nodes, but deemed high risk on the basis of one or more of the following (adverse histological sub type, age ≥ 45 years, multifocal, tumours greater than 4 cm in diameter, extra-thyroidal extension) is unclear.[55–57] In such cases **Personalised Decision Making** is recommended (Chapter 2.4, and Table 2.4) (**4**, **D**).

iii Unilateral PCCND does not appear to confer an advantage in reducing morbidity over bilateral surgery or post RRA Tg concentration. A prospective study comparing bilateral with unilateral PCCND showed no difference in mean postoperative basal/sTg, or permanent complications.[58] The addition of unilateral central neck dissection to total thyroidectomy compared with total thyroidectomy, alone does not result in lower Tg concentrations at 6 months post ablation.[47] Bilateral prophylactic central neck dissection will identify bilateral lymph node metastases in 13–50%[58,59,60] of patients and is the 'preferable' option for accurate staging.[46] Unilateral PCCND is not recommended (**2+**, **C**).

Prophylactic lateral neck lymph node dissection—The ATA Consensus Statement on the rationale for lateral neck dissection (2012) declared that prophylactic lateral neck dissection was unwarranted.[61] More recent studies have reported that prophylactic lateral neck dissection (levels III and IV) yields node positive disease in 8–23% of patients[46,62]; an increased risk of involvement of lateral neck nodes by tumour was associated with positive central compartment nodes/upper 1/3 tumours on multivariate analysis. A further study reports that patients who had previously undergone total thyroidectomy and PCCND, had a 6% lateral neck node recurrence rate at 5 years follow-up.[63] Protagonists of prophylactic lateral node dissection argue that it will identify and better stage the > 50% of patients with positive central neck nodes who will have metastatic nodes in levels III/IV. Those against, state there is no evidence to indicate that prophylactic lateral neck dissection improves survival or loco-regional control and over-treats 75% of patients.[46]

i Prophylactic lateral neck dissection in patients with no evidence of central compartment lymph node metastases, is not recommended (**2+**, **C**).

ii The evidence for an advantage of prophylactic lateral neck dissection compared to no prophylactic lateral neck dissection in patients with central compartment lymph involvement is unclear. In such cases **Personalised Decision Making** is recommended (Chapter 2.4) (**4**, **D**).

Therapeutic lymph node dissection

i Overt disease in the central compartment discovered prior to/at surgery should be treated by a therapeutic level VI/VII node dissection[64] (**3**, **D**).

ii If there is doubt as to the pathological nature of the nodes, frozen section has high sensitivity and specificity for detection of PTC.[65]**Good Practice Point** ☑

Patients with overt metastatic disease in the lateral neck will have clinical/radiological evidence of central neck lymph node metastases in more than 80% of cases.[70] Patients with lateral neck node metastases and no evidence of central neck node involvement on pre-operative imaging are high risk for histological evidence of level VI node metastases (>80%),[67,71]

iii When suspicious/clinically involved nodes in the lateral neck are apparent pre-operatively or are encountered at thyroidectomy, and confirmed by needle biopsy or frozen section, a therapeutic central and selective lateral neck dissection (levels IIa–Vb) is recommended, preserving the accessory nerve, sternocleidomastoid muscle and internal jugular vein.

Good Practice Point ☑

iv In the absence of clear indications, dissection of levels 1, IIb and Va is not recommended[69–71] (**2+**, **C**).

Surgery for follicular thyroid carcinoma (excluding oncocytic (Hürthle cell) follicular carcinoma). FNAC cannot at present distinguish follicular adenoma or benign hyperplastic nodules from carcinoma. Follicular (Thy3f) cytology usually mandates diagnostic hemithyroidectomy 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 (Chapter 5.2). Frozen section examination is unhelpful when the FNAC diagnosis is that of a follicular lesion (Thy3).[66,67]

i If definitive histology reveals a follicular adenoma or a hyperplastic nodule, no further treatment is required.

Good Practice Point ☑

ii Patients with follicular tumours >4 cm appear to have worse prognosis[68,72] and should be treated with total thyroidectomy (**3**, **D**).

Key recommendation

iii Patients with tumours ≤4 cm, in the absence of other adverse risk factors (age >45 years, widely invasive, lymph node/distant metastases, angioinvasion) appear to have an excellent prognosis.[73–75] It is recommended that such patients may be treated with hemithyroidectomy at the discretion of the MDT (**2−**, **C**).

iv Patients with tumours >1–≤4 cm and adverse risk factors (age >45 years, widely invasive, lymph node/distant metastases, angioinvasion) should be treated with total thyroidectomy (**2−**, **C**).

v Lymph node metastasis from follicular thyroid cancer is found in 1–8% of patients.[76] If there is preoperative or intraoperative suspicion of nodal disease, FNAC or frozen section should be performed prior to therapeutic node dissection.

Good Practice Point☑

Surgery for oncocytic (Hürthle cell) follicular carcinoma. There is conflicting evidence as to whether Hürthle cell carcinoma has equivalent[77,78] or worse[79] prognosis compared with follicular thyroid cancer, and worse prognosis compared with other types of DTC.[80] Lymph node metastases are reported to occur in 3–25% of cases, tumour size (>5 cm) and older age (>80 years) are risk factors for nodal disease.[81] Hürthle cell tumours are less likely to concentrate ^{131}I.

i Total thyroidectomy is recommended for oncocytic (Hürthle cell) carcinomas > 1 cm in diameter, (**2−**, **D**).

ii Patients with oncocytic (Hürthle cell) microcarcinoma (tumour size ≤1 cm) are reported to have an increased risk of distant metastases and reduced disease specific survival compared with patients with microPTC.[82] In the same study no survival benefit was identified for patients who underwent total thyroidectomy compared with patients treated with hemithyroidectomy. For patients with oncocytic (Hürthle cell) microcarcinoma **Personalised Decision Making** about hemi- or total thyroidectomy is recommended (Chapter 2.4, Table 2.4) (**4**, **D**).

iii Therapeutic lymph node dissection should be performed in patients with clinical/radiological evidence of lymph node involvement and pathological confirmation of metastasis

Good Practice Point ☑

The role of prophylactic node dissection is unclear. Loco-regional recurrence of Hürthle cell carcinoma is not associated with lymphoid tissue and most likely to result from spread via venous channels.[83]

i The evidence for an advantage of prophylactic neck dissection compared to no prophylactic neck dissection, in patients with Hurthle cell carcinomas is unclear. In such cases **Personalised Decision Making** is recommended (Chapter 2.4, Table 2.4) (**4**, **D**).

7.7. Emergency surgery

It is rare for emergency surgery to be needed, and in most cases a careful work-up of patients is achievable. Acute presentation of a patient with thyroid cancer and severe airway compromise requires urgent/immediate surgery.

7.8. Surgery for locally advanced disease

In patients with unilateral extra-thyroidal disease, preserving the nerve at the expense of risking residual macroscopic disease, does not carry adverse prognostic implications and is likely to result in normal nerve function[84,85] (**2−**, **C**). In patients with bilateral disease 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 on one or both sides (**4**, **D**).

i When pre-operative vocal cord examination has revealed no sign of recurrent laryngeal nerve involvement every attempt should be made to preserve the nerve/s (**4**, **D**).

ii In individual patients with locally advanced disease involving the upper aero-digestive tract, curative resection of the tracheal wall and/or oesophagus should be considered[86,87] (**2−**, **C**).

iii When radical curative surgery is not possible or agreed to by the patient, treatment with external beam radiotherapy may be appropriate (see Chapter 10).

7.9. Early post-surgical management

i Patients planned to receive RRA with recombinant human TSH (rhTSH) after total/near-total thyroidectomy, should commence on suppressive doses levothyroxine (2 mcg per kg body weight). Lower doses should be considered in obese patients. If a thyroid hormone withdrawal protocol is followed, triiodothyronine (T3) (usual adult dosage 20 mcg tds) may be used and should be stopped for 2 weeks before RRA (**4**, **D**).

Key recommendation

ii Serum calcium should be checked on the day after surgery (or earlier if symptoms occur) and levels further monitored if there is a high likelihood of hypocalcaemia (**3**, **D**).

iii If hypocalcaemia is detected, it should be treated as outlined in Chapter 11.2

iv It is recommended that patients with voice change after thyroidectomy, undergo laryngoscopy[13] (Chapter 11.1) (**2−**, **C**).

v Expert opinion recommends routine post-operative laryngoscopy in patients who have undergone thyroidectomy[13] (**4**, **D**).

vi A baseline postoperative serum Tg should be checked, preferably no earlier than 6 weeks after surgery (**2+, C**).

7.10. Management of other rare malignancies of the thyroid

Primary thyroid lymphoma[88].

i A clinical diagnosis or high index of suspicion of lymphoma may be confirmed by FNAC with the addition of immunophenotyping, although core biopsy and sometimes open biopsy may be required[89] (**3**, **D**).

ii Patients should be referred to the Lymphoma MDT

Good Practice Point ☑

Medullary thyroid cancer. This is discussed in Chapter 17.

Anaplastic thyroid cancer. This is discussed in Chapter 18.

References

1 Sosa, J.A., Bowman, H.M., Tielsch, J.M. *et al.* (1998) The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. *Annals of Surgery*, **228**, 320–330.

2 Sosa, J.A., Tuggle, C.T., Wang, T.S. *et al.* (2008) Clinical and economic outcomes of thyroid and parathyroid surgery in children. *Journal of Clinical Endocrinology and Metabolism*, **93**, 3058–3065.

3 Stavrakis, A.I., Ituarte, P.H., Ko, C.Y. *et al.* (2007) Surgeon volume as a predictor of outcomes in inpatient and outpatient endocrine surgery. *Surgery*, **142**, 887–899; discussion 887–899.

4 National Cancer Peer Review – National Cancer Action Team. Manual for Cancer Services: Head and Neck Measures Version 3.0. Available from: http://www.mycancertreatment.nhs.uk/wp-content/themes/mct/uploads/2012/09/resources_measures_HeadNeck_April2013.pdf (accessed 12 June 2014).

5 Kim, E., Park, J.S., Son, K.R. *et al.* (2008) Preoperative diagnosis of cervical metastatic lymph nodes in papillary thyroid carcinoma: comparison of ultrasound, computed tomography, and combined ultrasound with computed tomography. *Thyroid*, **18**, 411–418.

6 Choi, J.S., Kim, J., Kwak, J.Y. *et al.* (2009) Preoperative staging of papillary thyroid carcinoma: comparison of ultrasound imaging and CT. *AJR. American Journal of Roentgenology*, **193**, 871–878.

7 Yoon, J.H., Kim, J.Y., Moon, H.J. *et al.* (2011) Contribution of computed tomography to ultrasound in predicting lateral lymph node metastasis in patients with papillary thyroid carcinoma. *Annals of Surgical Oncology*, **18**, 1734–1741.

8 Consent: patients and doctors making decisions together. General Medical Council. Available from: http://www.gmc-uk.org/guidance/ethical_guidance/consent_guidance_index.asp (accessed 12 June 2014).

9 Anderson, O.A. & Wearne, I.M. (2007) Informed consent for elective surgery–what is best practice? *Journal of the Royal Society of Medicine*, **100**, 97–100.

10 Reinke, C.E., Hadler, R.A., Karakousis, G.C. *et al.* (2011) Does the presence of thyroid cancer increase the risk of venous thromboembolism in patients undergoing thyroidectomy? *Surgery*, **150**, 1275–1285.

11 Roy, M., Rajamanickam, V., Chen, H. *et al.* (2010) Is DVT prophylaxis necessary for thyroidectomy and parathyroidectomy? *Surgery*, **148**, 1163–1168; discussion 1168–1169.

12 National Institute for Clinical Excellence. (2010) Venous Thromboembolism: Reducing the Risk. http://guidance.nice.org.uk/CG92.

13 Chandrasekhar, S.S., Randolph, G.W., Seidman, M.D. *et al.* (2013) Clinical practice guideline: improving voice outcomes after thyroid surgery. *Otolaryngology – Head and Neck Surgery*, **148**(6 Suppl.), S1–37.

14 Alvarado, R., Sywak, M.S., Delbridge, L. *et al.* (2009) Central lymph node dissection as a secondary procedure for papillary thyroid cancer: is there added morbidity? *Surgery*, **145**, 514–518.

15 Shen, W.T., Ogawa, L., Ruan, D. *et al.* (2010) Central neck lymph node dissection for papillary thyroid cancer: comparison of complication and recurrence rates in 295 initial dissections and reoperations. *Archives of Surgery*, **145**, 272–275.

16 Clayman, G.L., Agarwal, G., Edeiken, B.S. *et al.* (2011) Long-term outcome of comprehensive central compartment dissection in patients with recurrent/persistent papillary thyroid carcinoma. *Thyroid*, **21**, 1309–1316.

17 Kim, M.K., Mandel, S.H., Baloch, Z. *et al.* (2004) Morbidity following central compartment reoperation for recurrent or persistent thyroid cancer. *Archives of Otolaryngology – Head and Neck Surgery*, **130**, 1214–1216.

18 Shah, M.D., Harris, L.D., Nassif, R.G. *et al.* (2012) Efficacy and safety of central compartment neck dissection for recurrent thyroid carcinoma. *Archives of Otolaryngology – Head and Neck Surgery*, **138**, 33–37.

19 Tufano, R.P., Bishop, J. & Wu, G. (2012) Reoperative central compartment dissection for patients with recurrent/persistent papillary thyroid cancer: efficacy, safety, and the association of the BRAF mutation. *Laryngoscope*, **122**, 1634–1640.

20 Lang, B.H., Ng, S.H., Lau, L. *et al.* (2013) A systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy. *Thyroid*, **23**, 1087–1098.

21 Hurtado-Lopez, L.M., Pacheco-Alvarez, M.I., Montes-Castillo Mde, L. *et al.* (2005) Importance of the intraoperative identification of the external branch of the superior laryngeal nerve during thyroidectomy: electromyographic evaluation. *Thyroid*, **15**, 449–454.

22 Seningen, J.L., Nassar, A. & Henry, M.R. (2012) Correlation of thyroid nodule fine-needle aspiration cytology with corresponding histology at Mayo Clinic, 2001-2007: an institutional experience of 1,945 cases. *Diagnostic Cytopathology*, **40**(Suppl. 1), E27–32.

23 Bilimoria, K.Y., Bentrem, D.J., Ko, C.Y. *et al.* (2007) Extent of surgery affects survival for papillary thyroid cancer. *Annals of Surgery*, **246**, 375–381; discussion 381–374.

24 Pelizzo, M.R., Boschin, I.M., Toniato, A. *et al.* (2007) Papillary thyroid carcinoma: 35-year outcome and prognostic factors in 1858 patients. *Clinical Nuclear Medicine*, **32**, 440–444.

25 Hay, I.D., McConahey, W.M. & Goellner, J.R. (2002) Managing patients with papillary thyroid carcinoma: insights gained from the Mayo Clinic's experience of treating 2,512 consecutive patients during 1940 through 2000. *Transactions of the American Clinical and Climatological Association*, **113**, 241–260.

26 Nixon, I.J., Ganly, I., Patel, S.G. *et al.* (2012) Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. *Surgery*, **151**, 571–579.

27 Matsuzu, K., Sugino, K., Masudo, K. *et al.* (2014) Thyroid Lobectomy for Papillary Thyroid Cancer: long-term Follow-up Study of 1,088 Cases. *World Journal of Surgery*, **38**, 68–79.

28 Hay, I.D., Grant, C.S., Taylor, W.F. *et al.* (1987) Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. *Surgery*, **102**, 1088–95.

29 Hassanain, M. & Wexler, M. (2010) Conservative management of well-differentiated thyroid cancer. *Canadian Journal of Surgery*, **53**, 109–118.

30 Mendelsohn, A.H., Elashoff, D.A., Abemayor, E. *et al.* (2010) Surgery for papillary thyroid carcinoma: is lobectomy enough? *Archives of Otolaryngology – Head and Neck Surgery*, **136**, 1055–1061.

31 Vivero, M., Kraft, S. & Barletta, J.A. (2013) Risk stratification of follicular variant of papillary thyroid carcinoma. *Thyroid*, **23**, 273–279.

32 Cherenko, S.M., Larin, O.S., Gorobeyko, M.B. *et al.* (2004) Clinical analysis of thyroid cancer in adult patients exposed to ionizing radiation due to the Chernobyl nuclear accident: 5-year comparative investigations based on the results of surgical treatment. *World Journal of Surgery*, **28**, 1071–1074.

33 Seaberg, R.M., Eski, S. & Freeman, J.L. (2009) Influence of previous radiation exposure on pathologic features and clinical outcome in patients with thyroid cancer. *Archives of Otolaryngology – Head and Neck Surgery*, **135**, 355–359.

34 Rubino, C., Cailleux, A.F., Abbas, M. *et al.* (2002) Characteristics of follicular cell-derived thyroid carcinomas occurring after external radiation exposure: results of a case control study nested in a cohort. *Thyroid*, **12**, 299–304.

35 Furlan, J.C. & Rosen, I.B. (2004) Prognostic relevance of previous exposure to ionizing radiation in well-differentiated thyroid cancer. *Langenbeck's Archives of Surgery*, **389**, 198–203.

36 Naing, S., Collins, B.J. & Schneider, A.B. (2009) Clinical behavior of radiation-induced thyroid cancer: factors related to recurrence. *Thyroid*, **19**, 479–485.

37 Haigh, P.I., Urbach, D.R. & Rotstein, L.E. (2005) Extent of thyroidectomy is not a major determinant of survival in low- or high-risk papillary thyroid cancer. *Annals of Surgical Oncology*, **12**, 81–89.

38 Zaydfudim, V., Feurer, I.D., Griffin, M.R. *et al.* (2008) The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. *Surgery*, **144**, 1070–1077; discussion 1077–1078.

39 Yang, L., Shen, W. & Sakamoto, N. (2013) Population-based study evaluating and predicting the probability of death resulting from thyroid cancer and other causes among patients with thyroid cancer. *Journal of Clinical Oncology*, **31**, 468–474.

40 Barczynski, M., Konturek, A., Stopa, M. *et al.* (2013) Prophylactic central neck dissection for papillary thyroid cancer. *British Journal of Surgery*, **100**, 410–418.

41 Costa, S, Giugliano, G, Santoro, L *et al.* (2009) Role of prophylactic central neck dissection in cN0 papillary thyroid cancer. *Acta Otorhinolaryngologica Italica*, **29**, 61–69.

42 Moo, T.A., McGill, J., Allendorf, J. *et al.* (2010) Impact of prophylactic central neck lymph node dissection on early recurrence in papillary thyroid carcinoma. *World Journal of Surgery*, **34**, 1187–1191.

43 Moreno, M.A., Edeiken-Monroe, B.S., Siegel, E.R. *et al.* (2012) In papillary thyroid cancer, preoperative central neck ultrasound detects only macroscopic surgical disease, but negative findings predict excellent long-term regional control and survival. *Thyroid*, **22**, 347–355.

44 Zuniga, S. & Sanabria, A. (2009) Prophylactic central neck dissection in stage N0 papillary thyroid carcinoma. *Archives of Otolaryngology – Head and Neck Surgery*, **135**, 1087–1091.

45 Wang, T.S., Evans, D.B., Fareau, G.G. *et al.* (2012) Effect of prophylactic central compartment neck dissection on serum thyroglobulin and recommendations for adjuvant radioactive iodine in patients with differentiated thyroid cancer. *Annals of Surgical Oncology*, **19**, 4217–4222.

46 Hartl, DM, Leboulleux, S, Al Ghuzlan, A *et al.* (2012) Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma. *Annals of Surgery*, **255**, 777–783.

47 Lang, B.H., Wong, K.P., Wan, K.Y. *et al.* (2012) Impact of routine unilateral central neck dissection on preablative and postablative stimulated thyroglobulin levels after total thyroidectomy in papillary thyroid carcinoma. *Annals of Surgical Oncology*, **19**, 60–67.

48 Popadich, A., Levin, O., Lee, J.C. *et al.* (2011) A multicenter cohort study of total thyroidectomy and routine central lymph node dissection for cN0 papillary thyroid cancer. *Surgery*, **150**, 1048–1057.

49 Wang, T.S., Cheung, K., Farrokhyar, F. *et al.* (2013) A meta-analysis of the effect of prophylactic central compartment neck dissection on locoregional recurrence rates in patients with papillary thyroid cancer. *Annals of Surgical Oncology*, **20**, 3477–3483.

50 Randolph, G.W., Duh, Q.Y., Heller, K.S. *et al.* (2012) The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid*, **22**, 1144–1152.

51 Nilubol, N., Zhang, L. & Kebebew, E. (2013) Multivariate analysis of the relationship between male sex, disease-specific survival, and features of tumor aggressiveness in thyroid cancer of follicular cell origin. *Thyroid*, **23**, 695–702.

52 Oyer, S.L., Smith, V.A. & Lentsch, E.J. (2013) Sex is not an independent risk factor for survival in differentiated thyroid cancer. *Laryngoscope*, **123**, 2913–2919.

53 Arora, N., Turbendian, H.K., Scognamiglio, T. *et al.* (2008) Extrathyroidal extension is not all equal: implications of macroscopic versus microscopic extent in papillary thyroid carcinoma. *Surgery*, **144**, 942–947; discussion 947–948.

54 Nixon, I.J., Ganly, I., Patel, S. *et al.* (2011) The impact of microscopic extrathyroid extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer. *Surgery*, **150**, 1242–1249.

55 Baek, S.K., Jung, K.Y., Kang, S.M. *et al.* (2010) Clinical risk factors associated with cervical lymph node recurrence in papillary thyroid carcinoma. *Thyroid*, **20**, 147–152.

56 Ito, Y., Kudo, T., Kobayashi, K. *et al.* (2012) Prognostic factors for recurrence of papillary thyroid carcinoma in the lymph nodes, lung, and bone: analysis of 5,768 patients with average 10-year follow-up. *World Journal of Surgery*, **36**, 1274–1278.

57 Nixon, I.J., Ganly, I., Patel, S.G. *et al.* (2013) Observation of clinically negative central compartment lymph nodes in papillary thyroid carcinoma. *Surgery*, **154**, 1166–1172; discussion 1172–1173.

58 Raffaelli, M., De Crea, C., Sessa, L. *et al.* (2012) Prospective evaluation of total thyroidectomy versus ipsilateral versus bilateral central neck dissection in patients with clinically node-negative papillary thyroid carcinoma. *Surgery*, **152**, 957–964.

59 Lee, KE, Chung, IY, Kang, E *et al.* (2013) Ipsilateral and contralateral central lymph node metastasis in papillary thyroid cancer: patterns and predictive factors of nodal metastasis. *Head and Neck*, **35**, 672–676.

60 Koo, B.S., Choi, E.C., Yoon, Y.H. *et al.* (2009) Predictive factors for ipsilateral or contralateral central lymph node metastasis in unilateral papillary thyroid carcinoma. *Annals of Surgery*, **249**, 840–844.

61 Stack, B.C. Jr, Ferris, R.L., Goldenberg, D. *et al.* (2012) American Thyroid Association consensus review and statement regarding the anatomy, terminology, and rationale for lateral neck dissection in differentiated thyroid cancer. *Thyroid*, **22**, 501–508.

62 Ducoudray, R., Tresallet, C., Godiris-Petit, G. *et al.* (2013) Prophylactic lymph node dissection in papillary thyroid carcinoma: is there a place for lateral neck dissection? *World Journal of Surgery*, **37**, 1584–1591.

63 Barczynski, M., Konturek, A., Stopa, M. *et al.* (2014) Nodal recurrence in the lateral neck after total thyroidectomy with prophylactic central neck dissection for papillary thyroid cancer. *Langenbeck's Archives of Surgery*, **399**, 237–244.

64 Wang, L.Y., Versnick, M.A., Gill, A.J. *et al.* (2013) Level VII is an important component of central neck dissection for papillary thyroid cancer. *Annals of Surgical Oncology*, **20**, 2261–2265.

65 Chae, B.J., Jung, C.K., Lim, D.J. *et al.* (2011) Performing contralateral central lymph node dissection in papillary thyroid carcinoma: a decision approach. *Thyroid*, **21**, 873–877.
66 Antic, T. & Taxy, J.B. (2013) Thyroid frozen section: supplementary or unnecessary? *American Journal of Surgical Pathology*, **37**, 282–286.
67 Lumachi, F., Borsato, S., Tregnaghi, A. *et al.* (2009) FNA cytology and frozen section examination in patients with follicular lesions of the thyroid gland. *Anticancer Research*, **29**, 5255–5257.
68 Mete, O. & Asa, S.L. (2011) Pathological definition and clinical significance of vascular invasion in thyroid carcinomas of follicular epithelial derivation. *Modern Pathology*, **24**, 1545–1552.
69 Caron, N.R., Tan, Y.Y., Ogilvie, J.B. *et al.* (2006) Selective modified radical neck dissection for papillary thyroid cancer-is level I, II and V dissection always necessary? *World Journal of Surgery*, **30**, 833–840.
70 Farrag, T., Lin, F., Brownlee, N. *et al.* (2009) Is routine dissection of level II-B and V-A necessary in patients with papillary thyroid cancer undergoing lateral neck dissection for FNA-confirmed metastases in other levels. *World Journal of Surgery*, **33**, 1680–1683.
71 Koo, B.S., Yoon, Y.H., Kim, J.M. *et al.* (2009) Predictive factors of level IIb lymph node metastasis in patients with papillary thyroid carcinoma. *Annals of Surgical Oncology*, **16**, 1344–1347.
72 D'Avanzo, A., Treseler, P., Ituarte, P.H. *et al.* (2004) Follicular thyroid carcinoma: histology and prognosis. *Cancer*, **100**, 1123–1129.
73 Goffredo, P., Cheung, K., Roman, S.A. *et al.* (2013) Can minimally invasive follicular thyroid cancer be approached as a benign lesion?: a population-level analysis of survival among 1,200 patients. *Annals of Surgical Oncology*, **20**, 767–772.
74 O'Neill, C.J., Vaughan, L., Learoyd, D.L. *et al.* (2011) Management of follicular thyroid carcinoma should be individualised based on degree of capsular and vascular invasion. *European Journal of Surgical Oncology*, **37**, 181–185.
75 Sugino, K., Kameyama, K., Ito, K. *et al.* (2012) Outcomes and prognostic factors of 251 patients with minimally invasive follicular thyroid carcinoma. *Thyroid*, **22**, 798–804.
76 Alfalah, H., Cranshaw, I., Jany, T. *et al.* (2008) Risk factors for lateral cervical lymph node involvement in follicular thyroid carcinoma. *World Journal of Surgery*, **32**, 2623–2626.
77 Sugino, K., Kameyama, K., Ito, K. *et al.* (2013) Does hurthle cell carcinoma of the thyroid have a poorer prognosis than ordinary follicular thyroid carcinoma? *Annals of Surgical Oncology*, **20**, 2944–2950.
78 Nagar, S., Aschebrook-Kilfoy, B., Kaplan, E.L. *et al.* (2013) Hurthle cell carcinoma: an update on survival over the last 35 years. *Surgery*, **154**, 1263–1271.
79 Kushchayeva, Y., Duh, Q.Y., Kebebew, E. *et al.* (2008) Comparison of clinical characteristics at diagnosis and during follow-up in 118 patients with Hurthle cell or follicular thyroid cancer. *American Journal of Surgery*, **195**, 457–462.
80 Goffredo, P., Roman, S.A. & Sosa, J.A. (2013) Hurthle cell carcinoma: a population-level analysis of 3311 patients. *Cancer*, **119**, 504–511.
81 Guerrero, M.A., Suh, I., Vriens, M.R. *et al.* (2010) Age and tumor size predicts lymph node involvement in Hurthle Cell Carcinoma. *Journal of Cancer*, **1**, 23–26.
82 Kuo, E.J., Roman, S.A. & Sosa, J.A. (2013) Patients with follicular and Hurthle cell microcarcinomas have compromised survival: a population level study of 22,738 patients. *Surgery*, **154**, 1246–1254.
83 Bishop, J.A., Wu, G., Tufano, R.P. *et al.* (2012) Histological patterns of locoregional recurrence in Hurthle cell carcinoma of the thyroid gland. *Thyroid*, **22**, 690–694.
84 Amini, K. & Frank, D.K. (2007) True vocal fold immobility in the setting of well-differentiated thyroid carcinoma: unusual illustrative cases and recommendations for operative strategy. *The Annals of Otology, Rhinology, and Laryngology*, **116**, 324–328.
85 Lang, B.H., Lo, C.Y., Wong, K.P. *et al.* (2013) Should an involved but functioning recurrent laryngeal nerve be shaved or resected in a locally advanced papillary thyroid carcinoma? *Annals of Surgical Oncology*, **20**, 2951–2957.
86 Tsukahara, K., Sugitani, I. & Kawabata, K. (2009) Surgical management of tracheal shaving for papillary thyroid carcinoma with tracheal invasion. *Acta Oto-Laryngologica*, **129**, 1498–1502.
87 Brauckhoff, M., Machens, A., Thanh, P.N. *et al.* (2010) Impact of extent of resection for thyroid cancer invading the aerodigestive tract on surgical morbidity, local recurrence, and cancer-specific survival. *Surgery*, **148**, 1257–1266.
88 Stein, S.A. & Wartofsky, L. (2013) Primary thyroid lymphoma: a clinical review. *Journal of Clinical Endocrinology and Metabolism*, **98**, 3131–3138.
89 Sangalli, G., Serio, G., Zampatti, C. *et al.* (2001) Fine needle aspiration cytology of primary lymphoma of the thyroid: a report of 17 cases. *Cytopathology*, **12**, 257–263.
90 Carty, S.E., Cooper, D.S., Doherty, G.M. *et al.* (2009) Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. *Thyroid*, **19**, 1153–1158.
91 Dralle, H. (2002) Lymph node dissection and medullary thyroid carcinoma. *British Journal of Surgery*, **89**, 1073–1075.

CHAPTER 8

8 Management of papillary microcarcinoma

'Microcarcinoma' is defined as a carcinoma of size of 10 mm and below in greatest dimension. Microcarcinomas constitute approximately 30% of all differentiated thyroid cancers and are largely responsible for the rise in incidence of thyroid cancer seen in many countries over the past decade.[1] Their management is one of the most controversial areas in thyroid cancer occupying a large proportion of MDT discussion time.

Microcarcinomas are usually an incidental finding, increasingly found on imaging or on histology of thyroidectomy specimens. 'Incidental' carcinoma refers to a tumour that is NOT the target lesion (clinically or radiologically) and is found on histological/microscopic examination of a thyroid removed for another reason, for example nodular goitre. These are nearly always of papillary thyroid carcinoma (microPTC) type but may occasionally be minimally invasive follicular carcinomas or rarely medullary thyroid carcinomas. Incidental microPTC are found in 2.2–49.9% (mostly 5–12%) of otherwise benign thyroid disease specimens,[2–13] and the rate of detection is significantly affected by the thoroughness of histology.[11]

8.1. Disease extent at diagnosis

Distant metastases are documented in 0–3% cases at diagnosis[14–25] However, lymph node involvement, is relatively common at 12.3–50% and the incidence depends on how intensely patients are investigated.[17,20,21,24–32]

8.2. Clinical outcome

The clinical outcome of microPTC is nearly always extremely good but there are a few exceptions.

Mortality. The mortality is very low with either no deaths[11,23,33–37] or only occasional deaths reported, ranging between 0.2% and 1% over 7.3–60 years of follow-up.[14–19,25,38,40–42] A meta-analysis which included 9379 patients identified 32 deaths (0.34%).[43]

Distant metastases. The risk of new distant metastases among 4096 patients from 15 pooled studies with a median follow-up between 3.7 and 11.2 years, was 0.4%.[43]

Local recurrence. Reported local recurrence rates are in 3.8–20%.[23,26,30,35,37,42,44–49] The risk of loco-regional recurrence among 5256 patients from 16 pooled studies with a median follow-up between 3.7 and 11.2 years, was 2.5%[43]). Recurrences are more likely to occur in neck lymph nodes than the thyroid bed, and occurred at any time after initial treatment during 20 years of follow-up.[25] Recurrences were amenable to successful treatment in most cases and did not adversely affect survival.[20]

8.3. Management

MicroPTC very rarely present with distant metastases, clinically apparent nodal disease, or extension beyond the thyroid capsule (pT3 or pT4). These cases should be managed as dictated by their disease stage (Chapter 7.2).

This section deals with microPTC which have no clinically evident disease in regional lymph nodes or distant metastases at the time of diagnosis.

Given that long-term survival is nearly 100%, the objective of any treatment is to reduce the risk of loco-regional recurrence (2.5%) and distant metastases (0.4%), while minimizing iatrogenic morbidity.[15,17,18,38,41]

Risk factors for recurrence or metastatic disease are shown in Table 8.1. A meta-analysis[43] identified the following risk factors: clinical (rather than incidental) presentation ($P < 0.0001$), multifocality ($P < 0.0001$) and lymph node involvement at diagnosis ($P < 0.0001$). The data on age as a risk factor are contradictory.[27,38]

The usual clinical scenarios where the MDT is called upon to provide recommendations for management are:

(a) The entire thyroid gland is in situ and an FNA of a suspicious lesion <1 cm in diameter has been reported as diagnostic of PTC, Thy5.
(b) A thyroid lobe has been removed for another reason (e.g. a follicular/Thy3f nodule) and it also contains one or more foci of microPTC.
(c) A total or near total thyroidectomy has been performed for another reason (e.g. Graves' disease or multinodular goitre) and it contains one or more foci of microPTC.

Thyroid surgery.

i Thyroid lobectomy is recommended for patients with a unifocal microPTC and no other risk factors (Table 8.1) **(2+, C).**
Key recommendation
ii The extent of thyroidectomy to be performed in patients with PTC and a history of neck irradiation is discussed in Chapter 7.2. No recommendation is made for patients with microPTC and only this additional risk factor **(4, D).**
iii Total thyroidectomy is recommended for patients with microPTC and familial non-medullary thyroid cancer (FNMTC) **(2+, C).**
iv Total thyroidectomy is recommended for patients with multifocal microPTC involving both lobes of the thyroid **(1−, A).**
v For all other patients with microPTC, the recommendation for type of surgery should be based on consideration of risk

Table 8.1. Risk factors for future recurrence and/or lymph node metastases in patients with thyroid microPTC (excluding patients who present with local or distant metastases)

Clinical and/or radiological features
Non-incidental[13,35,40,44,47,50–54]
PET-positive[55]
Histological features
Larger size (6–10 mm)[5,12,21,24,29,33,35,37,49,56–61]
Multifocal and/or bilateral[12,23,27,32,33,37,44,47,49,50,57,59,62–64]
Extra-thyroidal extension[11,12,23,27,31,32,37,42,44,50,51,54,55,57,65–67]
Poorly differentiated component[68,69]
Desmoplastic fibrosis and/or infiltrative growth pattern[70]

factors (Table 8.1) and **Personalised Decision Making** is recommended (Chapter 2.4, and Table 2.4) **(4, D).**

Lymph node surgery.

i Patients with papillary microcarcinoma who present with cervical node metastases require total thyroidectomy and therapeutic lymph node dissection of the involved nodal compartment/s as with PTC >T1a **(2−, D).**

ii Although prophylactic central compartment neck node dissection (PCCND) may not reduce the short term risk of local recurrence, PCCND should be considered in patients with tumours that are multifocal, pT3 and with extra-thyroidal spread. In such cases, **Personalised Decision Making** is recommended (Chapter 2.4, and Table 2.4) **(4, D).**

Recommendations for radioiodine remnant ablation (RRA). Risk assignment as described in Chapter 9.1 should dictate which patients may benefit from RRA.

Recommendations for TSH suppression. Risk assignment as described in Chapter 11.5 should dictate which patients may benefit from TSH suppression.

Recommendations for follow-up. Patients with unifocal microPTC and no other risk factors—Such patients who have undergone lobectomy, have a risk of dying of thyroid cancer similar to that of the general population,[71] a risk of recurrence of <2.5% and a risk of distant metastases of <0.4%. Given that for the general population the lifetime risk of developing any cancer is about 33% and the risk of dying from any cancer 28%[72] the benefits of screening for recurrence, are unlikely to outweigh the disadvantages.

i It is recommended therefore that such patients require no further follow-up for cancer care and can be discharged to the care of their GP **(4, D).**

ii The risk of developing hypothyroidism after thyroid lobectomy can be 15% or higher,[73–75] therefore annual biochemical surveillance in primary care is recommended[76] **(4, D).**

Patients with microPTC and additional risk factors—The follow-up of patients with microPTC and additional risk factors should be dictated by risk assignment after completion of treatment, as described in Chapter 2.

References

1 Hughes, D.T., Haymart, M.R., Miller, B.S. *et al.* (2011) The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years. *Thyroid*, **21**, 231–236.

2 de Matos, P.S., Ferreira, A.P. & Ward, L.S. (2006) Prevalence of papillary microcarcinoma of the thyroid in Brazilian autopsy and surgical series. *Endocrine Pathology*, **17**, 165–173.

3 Miccoli, P., Minuto, M.N., Galleri, D. *et al.* (2006) Incidental thyroid carcinoma in a large series of consecutive patients operated on for benign thyroid disease. *ANZ Journal of Surgery*, **76**, 123–126.

4 Dănilă, R., Karakas, E., Osei-Agyemang, T. *et al.* (2008) Outcome of incidental thyroid carcinoma in patients undergoing surgery for Graves' disease. *Revista Medico-Chirurgicala A Societatii de Medici si Naturalisti din Iasi*, **112**, 115–118.

5 Pakdaman, M.N., Rochon, L., Gologan, O. *et al.* (2008) Incidence and histopathological behavior of papillary microcarcinomas: study of 429 cases. *Otolaryngology – Head and Neck Surgery*, **139**, 718–722.

6 Fernando, R., Mettananda, D.S. & Kariyakarawana, L. (2009) Incidental occult carcinomas in total thyroidectomy for benign diseases of the thyroid. *Ceylon Medical Journal*, **54**, 4–6.

7 Gul, K., Di Ri Koc, A., Ki Yak, G. *et al.* (2009) Thyroid carcinoma risk in patients with hyperthyroidism and role of preoperative cytology in diagnosis. *Minerva Endocrinologica*, **34**, 281–288.

8 Bradly, D.P., Reddy, V., Prinz, R.A. *et al.* (2009) Incidental papillary carcinoma in patients treated surgically for benign thyroid diseases. *Surgery*, **146**, 1099–1104.

9 Gul, K., Dirikoc, A., Kiyak, G. *et al.* (2010) The association between thyroid carcinoma and Hashimoto's thyroiditis: the ultrasonographic and histopathologic characteristics of malignant nodules. *Thyroid*, **20**, 873–878.

10 Botrugno, I., Lovisetto, F., Cobianchi, L. *et al.* (2011) Incidental carcinoma in multinodular goiter: risk factors. *American Surgeon*, **77**, 1553–1558.

11 Neuhold, N., Schultheis, A., Hermann, M. *et al.* (2011) Incidental papillary microcarcinoma of the thyroid – further evidence of a very low malignant potential: a retrospective clinicopathological study with up to 30 years of follow-up. *Annals of Surgical Oncology*, **18**, 3430–3436. Erratum in: Ann Surg Oncol. 2011;18:3528..

12 Vasileiadis, I., Karakostas, E., Charitoudis, G. *et al.* (2012) Papillary thyroid microcarcinoma: clinicopathological characteristics and implications for treatment in 276 patients. *European Journal of Clinical Investigation*, **42**, 657–664.

13 Dunki-Jacobs, E., Grannan, K., McDonough, S. *et al.* (2012) Clinically unsuspected papillary microcarcinomas of the thyroid: a common finding with favorable biology? *American Journal of Surgery*, **203**, 140–144.

14 Baudin, E., Travagli, J.P., Ropers, J. *et al.* (1998) Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience. *Cancer*, **83**, 553–559.

15 Hay, I.D., Grant, C.S., van Heerden, J.A. *et al.* (1992) Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. *Surgery*, **112**, 1139–1146; discussion 1146–1147.

16 Chow, S.M., Law, S.C., Chan, J.K. *et al.* (2003) Papillary microcarcinoma of the thyroid-Prognostic significance of lymph node metastasis and multifocality. *Cancer*, **98**, 31–40.
17 Ito, Y., Uruno, T., Nakano, K. *et al.* (2003) An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. *Thyroid*, **13**, 381–387.
18 Noguchi, S., Yamashita, H., Murakami, N. *et al.* (1996) Small carcinomas of the thyroid. A long-term follow-up of 867 patients. *Archives of Surgery*, **131**, 187–191.
19 Yamashita, H., Noguchi, S., Murakami, N. *et al.* (1997) Extracapsular invasion of lymph node metastasis is an indicator of distant metastasis and poor prognosis in patients with thyroid papillary carcinoma. *Cancer*, **80**, 2268–2272.
20 Corapcioglu, D., Sak, S.D., Delibasi, T. *et al.* (2006) Papillary microcarcinomas of the thyroid gland and immunohistochemical analysis of expression of p53 protein in papillary microcarcinomas. *Journal of Translational Medicine*, **4**, 28.
21 Lee, J., Rhee, Y., Lee, S. *et al.* (2006) Frequent, aggressive behaviors of thyroid microcarcinomas in korean patients. *Endocrine Journal*, **53**, 627–632.
22 Lo, C.Y., Chan, W.F., Lang, B.H. *et al.* (2006) Papillary microcarcinoma: is there any difference between clinically overt and occult tumors? *World Journal of Surgery*, **30**, 759–766.
23 Küçük, N.O., Tari, P., Tokmak, E. *et al.* (2007) Treatment for microcarcinoma of the thyroid–clinical experience. *Clinical Nuclear Medicine*, **32**, 279–281.
24 Lim, D.J., Baek, K.H., Lee, Y.S. *et al.* (2007) Clinical, histopathological, and molecular characteristics of papillary thyroid microcarcinoma. *Thyroid*, **17**, 883–888.
25 Hay, I.D., Hutchinson, M.E., Gonzalez-Losada, T. *et al.* (2008) Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. *Surgery*, **144**, 980–987.
26 Cheema, Y., Olson, S., Elson, D. *et al.* (2006) What is the biology and optimal treatment for papillary microcarcinoma of the thyroid? *Journal of Surgical Research*, **134**, 160–162.
27 Gülben, K., Berberoğlu, U., Celen, O. *et al.* (2008) Incidental papillary microcarcinoma of the thyroid–factors affecting lymph node metastasis. *Langenbeck's Archives of Surgery*, **393**, 25.
28 Kwak, J.Y., Kim, E.K., Kim, M.J. *et al.* (2009) Papillary microcarcinoma of the thyroid: predicting factors of lateral neck node metastasis. *Annals of Surgical Oncology*, **16**, 1348–1355.
29 Lim, Y.C., Choi, E.C., Yoon, Y.H. *et al.* (2009) Central lymph node metastases in unilateral papillary thyroid microcarcinoma. *British Journal of Surgery*, **96**, 253–257.
30 Park, Y.J., Kim, Y.A., Lee, Y.J. *et al.* (2010) Papillary microcarcinoma in comparison with larger papillary thyroid carcinoma in BRAF(V600E) mutation, clinicopathological features, and immunohistochemical findings. *Head and Neck*, **32**, 38–45.
31 Zheng, X., Wei, S., Han, Y. *et al.* (2013) Papillary microcarcinoma of the thyroid: clinical characteristics and BRAF(V600E) mutational status of 977 cases. *Annals of Surgical Oncology*, **20**, 2266–2273.
32 So, Y.K., Son, Y.I., Hong, S.D. *et al.* (2010) Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. *Surgery*, **148**, 526–531.
33 Roti, E., Rossi, R., Trasforini, G. *et al.* (2006) Clinical and histological characteristics of papillary thyroid microcarcinoma: results of a retrospective study in 243 patients. *Journal of Clinical Endocrinology and Metabolism*, **91**, 2171–2178.
34 Soyluk, O., Selcukbiricik, F., Erbil, Y. *et al.* (2008) Prognostic factors in patients with papillary thyroid carcinoma. *Journal of Endocrinological Investigation*, **31**, 1032–1037.
35 Arora, N., Turbendian, H.K., Kato, M.A. *et al.* (2009) Papillary thyroid carcinoma and microcarcinoma: is there a need to distinguish the two? *Thyroid*, **19**, 473–477.
36 Durante, C., Attard, M., Torlontano, M. *et al.* (2010) Identification and optimal postsurgical follow-up of patients with very low-risk papillary thyroid microcarcinomas. *Journal of Clinical Endocrinology and Metabolism*, **95**, 4882–4888.
37 Giordano, D., Gradoni, P., Oretti, G. *et al.* (2010) Treatment and prognostic factors of papillary thyroid microcarcinoma. *Clinical Otolaryngology*, **35**, 118–124.
38 Yu, X.M., Wan, Y., Sippel, R.S. *et al.* (2011) Should all papillary thyroid microcarcinomas be aggressively treated? An analysis of 18,445 cases. *Annals of Surgery*, **254**, 653–660.
39 Pelizzo, M.R., Boschin, I.M., Toniato, A. *et al.* (2006) Papillary thyroid microcarcinoma (PTMC): prognostic factors, management and outcome in 403 patients. *European Journal of Surgical Oncology*, **32**, 1144–1148.
40 Lin, J.D., Kuo, S.F., Chao, T.C. *et al.* (2008) Incidental and non-incidental papillary thyroid microcarcinoma. *Annals of Surgical Oncology*, **15**, 2287–2292.
41 Lin, H.W. & Bhattacharyya, N. (2009) Survival impact of treatment options for papillary microcarcinoma of the thyroid. *The Laryngoscope*, **119**, 1983–1987.
42 Mercante, G., Frasoldati, A., Pedroni, C. *et al.* (2009) Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. *Thyroid*, **19**, 707–716.
43 Roti, E., degli Uberti, E.C., Bondanelli, M. *et al.* (2008) Thyroid papillary microcarcinoma: a descriptive and meta-analysis study. *European Journal of Endocrinology*, **159**, 659–673.
44 Ardito, G., Revelli, L., Giustozzi, E. *et al.* (2013) Aggressive papillary thyroid microcarcinoma: prognostic factors and therapeutic strategy. *Clinical Nuclear Medicine*, **38**, 25–28.
45 Ito, Y., Higashiyama, T., Takamura, Y. *et al.* (2007) Prognosis of patients with benign thyroid diseases accompanied by incidental papillary carcinoma undetectable on preoperative imaging tests. *World Journal of Surgery*, **31**, 1672–1676.
46 Kim, T.Y., Hong, S.J., Kim, J.M. *et al.* (2008) Prognostic parameters for recurrence of papillary thyroid microcarcinoma. *BMC Cancer*, **8**, 296.
47 Lombardi, C.P., Bellantone, R., De Crea, C. *et al.* (2010) Papillary thyroid microcarcinoma: extrathyroidal extension, lymph node metastases, and risk factors for recurrence in a high prevalence of goiter area. *World Journal of Surgery*, **34**, 1214–1221.
48 Moon, H.J., Kim, E.K., Chung, W.Y. *et al.* (2011) Minimal extrathyroidal extension in patients with papillary thyroid microcarcinoma: is it a real prognostic factor? *Annals of Surgical Oncology*, **18**, 1916–1923.
49 Buffet, C., Golmard, J.L., Hoang, C. *et al.* (2012) Scoring system for predicting recurrences in patients with papillary thyroid microcarcinoma. *European Journal of Endocrinology*, **167**, 267–275.
50 Page, C., Biet, A., Boute, P. *et al.* (2009) Aggressive papillary thyroid microcarcinoma. *European Archives of Oto-Rhino-Laryngology*, **266**, 1959–1963.
51 Pisanu, A., Reccia, I., Nardello, O. *et al.* (2009) Risk factors for nodal metastasis and recurrence among patients with papillary thyroidmicrocarcinoma: differences in clinical relevance between

nonincidental and incidental tumors. *World Journal of Surgery*, **33**, 460–468.
52 Lin, J.D. (2010) Increased incidence of papillary thyroid microcarcinoma with decreased tumor size of thyroid cancer. *Medical Oncology*, **27**, 510–518.
53 Besic, N., Zgajnar, J., Hocevar, M. *et al.* (2009) Extent of thyroidectomy and lymphadenectomy in 254 patients with papillary thyroid microcarcinoma: a single-institution experience. *Annals of Surgical Oncology*, **16**, 920–928.
54 Sugitani, I., Toda, K., Yamada, K. *et al.* (2010) Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. *World Journal of Surgery*, **34**, 1222–1231.
55 Yun, M., Noh, T.W., Cho, A. *et al.* (2010) Visually discernible [18F]fluorodeoxyglucose uptake in papillary thyroid microcarcinoma: a potential new risk factor. *Journal of Clinical Endocrinology and Metabolism*, **95**, 3182–3188.
56 Kuo, S.F., Chao, T.C., Chang, H.Y. *et al.* (2011) Prognostic evaluation of patients with multicentric papillary thyroid microcarcinoma. *Journal of the Formosan Medical Association*, **110**, 511–517.
57 Gershinsky, M., Barnett-Griness, O., Stein, N. *et al.* (2012) Total versus hemithyroidectomy for microscopic papillary thyroid cancer. *Journal of Endocrinological Investigation*, **35**, 464–468.
58 Friguglietti, C.U., Dutenhefner, S.E., Brandão, L.G. *et al.* (2011) Classification of papillary thyroid microcarcinoma according to size and fine-needle aspiration cytology: behavior and therapeutic implications. *Head and Neck*, **33**, 696–701.
59 Zhang, L., Wei, W.J., Ji, Q.H. *et al.* (2012) Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. *Journal of Clinical Endocrinology and Metabolism*, **97**, 1250–1257.
60 Garrel, R., Tripodi, C., Cartier, C. *et al.* (2011) Cervical lymphadenopathies signaling thyroid microcarcinoma. Case study and review of the literature. *European Annals of Otorhinolaryngology, Head and Neck Diseases*, **128**, 115–119.
61 Lee, K.J., Cho, Y.J., Kim, S.J. *et al.* (2011) Analysis of the clinicopathologic features of papillary thyroid microcarcinoma based on 7-mm tumor size. *World Journal of Surgery*, **35**, 318–323.
62 Lin, J.D., Chao, T.C., Hsueh, C. *et al.* (2009) High recurrent rate of multicentric papillary thyroid carcinoma. *Annals of Surgical Oncology*, **16**, 2609–2616.
63 Koo, B.S., Lim, H.S., Lim, Y.C. *et al.* (2010) Occult contralateral carcinoma in patients with unilateral papillary thyroid microcarcinoma. *Annals of Surgical Oncology*, **17**, 1101–1105.
64 Connor, M.P., Wells, D. & Schmalbach, C.E. (2011) Variables predictive of bilateral occult papillary microcarcinoma following total thyroidectomy. *Otolaryngology – Head and Neck Surgery*, **144**, 210–215.
65 Kim, K.-E., Kim, E.-K., Yoon, J.H. *et al.* (2013) Preoperative prediction of central lymph node metastasis in thyroid papillary microcarcinoma using clinicopathologic and sonographic features. *World Journal of Surgery*, **37**, 385–391.
66 Jacquot-Laperrière, S., Timoshenko, A.P., Dumollard, J.M. *et al.* (2007) Papillary thyroid microcarcinoma: incidence and prognostic factors. *European Archives of Oto-Rhino-Laryngology*, **264**, 935–939.
67 Nixon, I.J., Ganly, I., Patel, S. *et al.* (2011) The impact of microscopic extrathyroid extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer. *Surgery*, **150**, 1242–1249.
68 Ghossein, R., Ganly, I., Biagini, A. *et al.* (2014) Prognostic factors in papillary microcarcinoma with emphasis on histologic subtyping: a clinicopathologic study of 148 cases. *Thyroid*, **24**, 245–253.
69 Bernstein, J., Virk, R.K., Hui, P. *et al.* (2013) Tall cell variant of papillary thyroid microcarcinoma: clinicopathologic features with BRAF V600E mutational analysis. *Thyroid*, **23**, 1525–1531.
70 Koperek, O., Asari, R., Niederle, B. *et al.* (2011) Desmoplastic stromal reaction in papillary thyroid microcarcinoma. *Histopathology*, **58**, 919–924.
71 http://www.cancer.org/cancer/cancerbasics/lifetime-probability-of-developing-or-dying-from-cancer
72 http://www.cancerresearchuk.org/cancer-info/cancerstats/incidence/risk/statistics-on-the-risk-of-developing-cancer
73 Stoll, S.J., Pitt, S.C., Liu, J. *et al.* (2009) Thyroid hormone replacement after thyroid lobectomy. *Surgery*, **146**, 554–558.
74 Johner, A., Griffith, O.L., Walker, B. *et al.* (2011) Detection and management of hypothyroidism following thyroid lobectomy: evaluation of a clinical algorithm. *Annals of Surgical Oncology*, **18**, 2548–2554.
75 Balentine, C.J., Domingo, R.P., Patel, R. *et al.* (2013) Thyroid lobectomy for indeterminate FNA: not without consequences. *Journal of Surgical Research*, **184**, 189–192.
76 UK Guidelines for the Use of Thyroid Function Tests (2006) http://www.british-thyroid-association.org/info-for-patients/Docs/TFT_guideline_final_version_July_2006.pdf.

CHAPTER 9

9 Radioiodine remnant ablation and therapy for differentiated thyroid cancer

Following a total or near total thyroidectomy, some ^{131}I uptake is usually demonstrable in the thyroid bed. ^{131}I-induced destruction of this residual thyroid tissue is known as 'radioiodine remnant ablation' (RRA). This term should not be used to describe treatment for known residual local or metastatic disease. 'Radioiodine therapy' refers to administration of ^{131}I with the intention to treat residual, recurrent or metastatic disease.

The principles and procedures are similar for the administration of ^{131}I for RRA or therapy purposes.

9.1. Post-operative RRA

RRA has been used for many years as an adjunct to near total/total thyroidectomy in patients with differentiated thyroid cancer (DTC). All the evidence available of the effects of RRA on cancer recurrence and survival is retrospective. The potential benefits of RRA need to be balanced against risks and the inconvenience imposed by the procedure on an individualised basis.

Advantages of RRA.

- Possible prolonged survival[1–3]
- Eradication of all residual thyroid cells postoperatively with subsequent reduced risk of local and distant tumour recurrence[3–5]
- Reassurance to patients provided by the knowledge that serum Tg is undetectable and neck US or diagnostic iodine scan imaging is negative, implying that all thyroid tissue has been destroyed
- Increased sensitivity of Tg monitoring facilitating early detection of recurrent or metastatic disease[6,7]
- Increased sensitivity of subsequent iodine scanning if required

Disadvantages of RRA (also see section 9.5).

- Need to avoid pregnancy (6 months) or fathering a child (4 months) (Chapter 14)
- Slightly increased risk of miscarriage in the first year after RRA (Chapter 14)
- Hospital stay in isolation
- Need to maintain a safe distance from others for a short period after treatment
- Painful thyroiditis (rare)
- Radiation cystitis, gastritis, bleeding or oedema from metastases (rare)
- Nausea
- Exposure to potential side-effects of recombinant human TSH (rhTSH) (rare) or to a short period of hypothyroidism
- Sialadenitis
- Xerostomia
- Dysgeusia
- Pulmonary fibrosis (rare)
- Second malignancy (risk may be higher than previously thought)[8]

Current evidence suggests that some patients with DTC will benefit from RRA, while others will not. For a significant group of patients the evidence is inadequate or conflicting, so that clear recommendations cannot be made.[1,4,5,8,9] For the purpose of RRA patients can be classified into three categories: (a) definite indications for RRA (b) uncertain indications for RRA (c) no indication for RRA (Fig. 9.1).

Definite indications, uncertain indications and no indication for RRA. The decision about RRA can be difficult for the MDT and the patient as the evidence is incomplete and the aim is to individualise treatment. Table 9.1 summarises the evidence for RRA.[10] Fig. 9.1 summarises the indications for RRA.

i The MDT decision about RRA should be individualised.
Good Practice Point ☑

ii Patients who have had less than a total or near-total thyroidectomy should be considered for further surgery before RRA (**4**, **D**).

iii A clinical oncologist or nuclear medicine physician with expertise and an interest in the management of DTC should supervise this treatment and be a core member of the MDT (**4**, **D**).
Key recommendation

'Definite' and 'no indications' for RRA—

i Patients in the 'definite indications' category (tumour >4 cm, or any tumour size with gross extra-thyroidal extension (pT4), or distant metastases present) should be advised to receive RRA (**2+**, **C**).
Key recommendation

ii Patients in the 'no indications' category (tumour ≤1 cm unifocal or multifocal, and on histology classical papillary or follicular variant or follicular minimally invasive without angioinvasion and no invasion of thyroid capsule) should be advised against receiving RRA (**2+**, **C**).
Key recommendation

iii Patients advised to receive RRA should be counselled so that they understand the rationale for RRA in order that they are

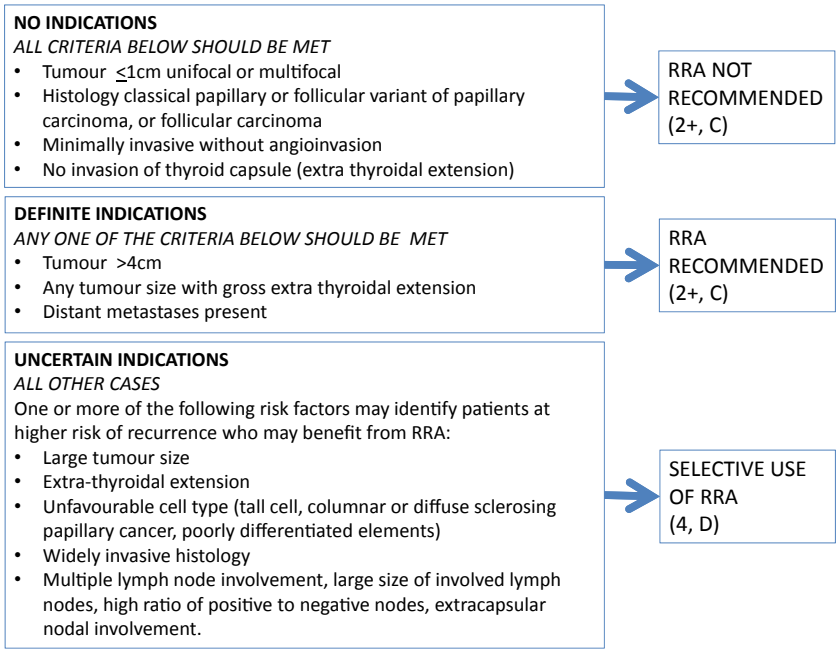


Fig. 9.1 Indications for RRA.

able to make an informed decision based on the risks and benefits.

Good Practice Point ☑

iv The acute and late side effects of ^{131}I (also see section 9.5) should be discussed with patients planned to receive RRA.

Good Practice Point ☑

'Uncertain indications' for RRA—Patients in the 'uncertain indications' category may or may not derive a benefit from RRA. Factors that may tip the balance in favour of RRA are: large tumour size, extra-thyroidal extension, presence of unfavourable histological cell type (tall cell, or columnar cell papillary thyroid cancer (PTC), diffuse sclerosing PTC, poorly

Table 9.1. Summary of strength of evidence of benefit of RRA in patients with DTC

		Expected benefit				
Factors	Description	Decreased risk of death	Decreased risk of recurrence	May facilitate initial staging and follow up	RRA usually recommended	Strength of evidence
T1	1 cm or less, intra-thyroidal or microscopic multifocal	No	No	Yes	No	**2++, B**
	1–2 cm, intra-thyroidal	No	Conflicting data*	Yes	Selective use*	Insufficient evidence to advise for or against
T2	>2–4 cm, intra-thyroidal	No	Conflicting data*	Yes	Selective use*	**4, D**
T3	>4 cm					
	<45 years old	No	Conflicting data*	Yes	Yes	**2+, D**
	≥45 years old	Yes	Yes	Yes	Yes	**2+, C**
	Any size, any age, minimal extra-thyroidal extension	No	Inadequate data*	Yes	Selective use*	Insufficient evidence to advise for or against
T4	Any size with gross extra-thyroidal extension	Yes	Yes	Yes	Yes	**2+, C**
N0	No metastatic nodes documented	No	No	Yes	No	Insufficient evidence to advise for or against
N1	<45 years old	No	Conflicting data*	Yes	Selective use*	**4, D**
	≥45 years old	Conflicting data*	Conflicting data*	Yes	Selective use*	**4, D**
M1	Distant metastases present	Yes	Yes	Yes	Yes	**2++, B**

*Because of either conflicting or inadequate data, recommendations cannot be made either for or against RRA for this entire subgroup. However, selected patients within this subgroup with higher risk features may benefit from RRA.

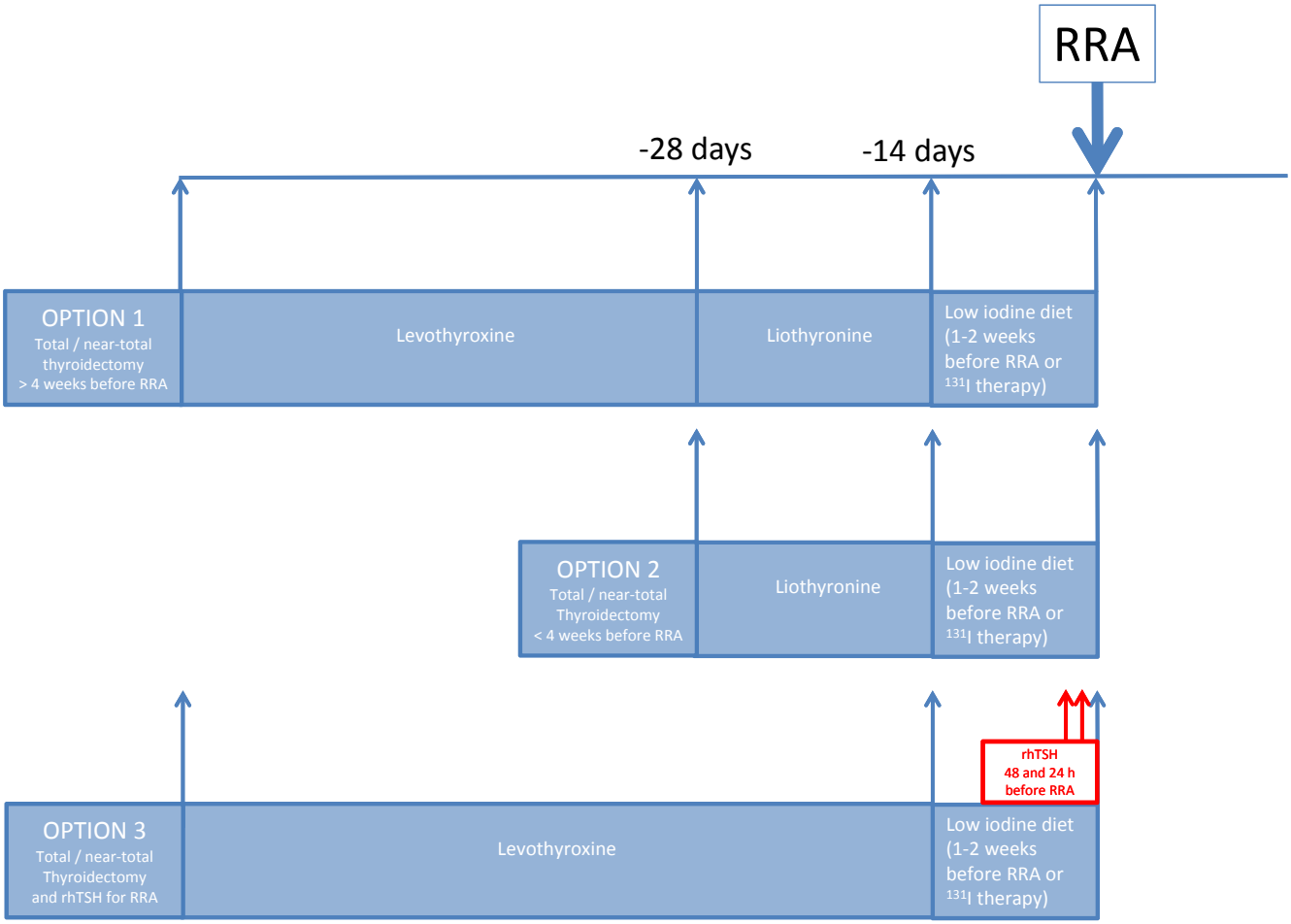


Fig. 9.2 Different methods of preparation for RRA.

differentiated elements), widely invasive histology, multiple metastatic lymph nodes, resected metastatic lymph nodes large in size, high ratio of positive to negative nodes, extra-capsular nodal involvement (Fig. 9.1) (Chapter 2.4 and Table 2.4).

i For patients within the 'uncertain indications' category, a **Personalised Decision Making** approach should be adopted (Chapter 2.4 and Table 2.4) (**4**, **D**).

9.2. Preparation for RRA or ^{131}I therapy

i Prior to considering RRA the patient should have undergone total thyroidectomy performed by an experienced thyroid surgeon who is a core member of the thyroid cancer MDT (Chapter 7) (Fig. 9.2).
Good Practice Point ☑

ii The patient should be seen by an appropriate member of the MDT (an Administration of Radioactive Substances Advisory Committee (ARSAC) Certificate holder), preferably in a multidisciplinary clinic, for assessment and discussion about the indication for RRA (or ^{131}I therapy). Informed consent should be obtained from the patient before treatment.
Good Practice Point ☑
Key recommendation

iii Patients should be offered written information (Appendix 5, Patient Information Leaflet 4) and introduced to a Clinical Nurse Specialist who will act as their Keyworker.
Good Practice Point ☑

iv RRA and ^{131}I therapy must be administered by centres suitably equipped and certified for the purpose.[11]
Good Practice Point ☑
Key recommendation

Exogenous iodine. A diet rich in iodine, exposure to iodinated intravenous contrast and treatment with amiodarone (a drug high in iodine content), may compromise the efficacy of ^{131}I. Dietary restrictions applicable in some countries may not be relevant to the UK where there is relative mild iodine deficiency.[12–16] There is very limited evidence on how long patients should observe a low iodine diet, how long RRA or ^{131}I therapy should be deferred for after intravenous iodinated contrast[17] or after discontinuation of amiodarone.[18] The recommendations below reflect expert opinion.

i Patients should be advised to adopt a low iodine diet for 1–2 weeks prior to RRA or ^{131}I therapy (**4**, **D**).

ii The significant iodide load resulting from contrast enhanced CT may compromise ^{131}I uptake in a thyroid remnant or in (relatively) poorly functioning thyroid metastases. For this reason, a minimum interval of 8 weeks is recommended between contrast enhanced radiological investigations and ^{131}I administration (**4**, **D**).

iii RRA or ^{131}I therapy should be avoided if the patient is currently taking amiodarone or has taken amiodarone within the previous 12 months (**4**, **D**).

Recombinant human TSH (rhTSH) and RRA or therapy. Randomised trials have shown that RRA is equally successful after rhTSH, as after THW for selected patients with DTC.[19,33]

The use of rhTSH is also associated with better quality of life[21,22,80] and reduces radiation exposure to normal tissues compared to THW.[20,24–26] rhTSH has not been evaluated in randomised controlled trials for RRA in patients at high risk of recurrence, or for the treatment of recurrent or metastatic DTC and is not currently licensed for this purpose. However, observational studies suggest that rhTSH may be as effective as THW in RRA of patients with high risk disease, or patients with recurrence or metastases.[27,28]

i rhTSH is the recommended method of preparation for RRA in patients who have the following characteristics: pT1 to T3, pN0 or NX or N1, and M0 and R0 (no microscopic residual disease) (**1++**, **A**).

Key recommendation

ii Whether THW is preferable to the use of rhTSH for RRA of high risk patients or patients with recurrent or metastatic disease, is uncertain. rhTSH is the safer alternative when there is a medical reason why THW is contraindicated.[29] In other cases, a **Personalised Decision Making** approach is recommended (Chapter 2.4) (**4**, **D**).

iii If rhTSH is unavailable or not indicated, alternative methods of preparation are as follows (Fig. 9.2):

- If RRA is planned within 3–4 weeks of surgery liothyronine should be commenced on the day after surgery and withdrawn 14 days before RRA (**4**, **D**).
- If the period between surgery and RRA is expected to be longer than 4 weeks, patients should be commenced on thyroid hormone replacement. This may be levothyroxine, in which case it should be substituted with liothyronine 28 days prior to RRA or therapy and then Liothyronine should be withdrawn 14 days prior to RRA or therapy. Alternatively liothyronine can be commenced immediately after surgery and withdrawn 14 days prior to RRA or therapy (**4**, **D**).

iv Measurement of stimulated thyroglobulin (sTg) after rhTSH and RRA or ^{131}I therapy, requires handling of a radioactive blood sample. Arrangement must be in place with the local laboratory, for handling and storage (if necessary) of the sample prior to assay.

Good Practice Point ☑

v If a patient has undergone THW, serum TSH and Tg should be measured immediately prior to ^{131}I administration (**4**, **D**).

vi A pre-ablation scan is not indicated routinely if the patient has had optimal surgery. If there is any doubt over completeness of surgery or radiological evidence of a large remnant, further resection should be discussed before proceeding to RRA (**4**, **D**)

vii Pregnancy must be excluded before RRA or ^{131}I therapy is administered in women of reproductive age (Chapter 14) (**3**, **D**).

Key recommendation

viii The dopamine agonist cabergoline can be considered to suppress lactation, if necessary[30] (**4**, **D**).

ix Breastfeeding must be discontinued at least 8 weeks before RRA or ^{131}I therapy to avoid breast irradiation and should not be resumed until after a subsequent pregnancy (**4**, **D**).

Key recommendation

x Pre-treatment sperm banking should be considered in male patients likely to have more than two high activity ^{131}I therapies[31,32] (**4**, **D**).

xi Adequate hydration, regular emptying of the bladder and avoidance of constipation should be encouraged at the time of RRA or ^{131}I therapy and for several days afterwards to reduce radiation exposure to the pelvic organs (**4**, **D**).

xii Excretion of ^{131}I is mainly via the renal system therefore adequate renal function should be demonstrated prior to administration (**4**, **D**).

9.3. Activity of ^{131}I

^{131}I Ablation activity. Results from two large multicentre randomised trials[19,33] have shown that 1·1 GBq of ^{131}I was as effective as 3·7 GBq in ablating the thyroid remnant in the low and intermediate risk group, while adverse events were fewer in the 1·1 GBq group. In these studies all patients had undergone total thyroidectomy and had an R0 (no microscopic residual disease) resection. Most patients were staged pT1 N0 and pT2 N0. One of the trials[19] included patients with pT3 tumours, and patients with N1 disease, who were ablated successfully with 1·1 GBq. A recent meta-analysis found no difference in efficacy between 1·1 and 3·7 GBq.[34]

i Patients with pT1-2, N0 with R0 resection should receive 1·1 GBq (**1++**, **A**).

ii Patients with pT3 and/or N1 disease, the final choice of ^{131}I activity should be decided by the MDT on an individual case basis taking all prognostic factors into consideration (**4**, **D**).

^{131}I therapy activity. The optimal ^{131}I therapeutic activity for persistent neck disease or metastatic disease is uncertain. Most of the evidence for a benefit of ^{131}I therapy in patients with DTC derives from studies where empirical activities of ^{131}I were used.[6,7,23,35–40] The role of dosimetry and its impact on clinical outcomes, compared to empirical use of ^{131}I therapy is unclear.[41–43]

i Administration of empirical activities is recommended (**2+**, **C**).
ii Quantitative imaging based dosimetry with ^{131}I SPECT-CT or ^{124}I PET assessment particularly in the metastatic setting, remains within the research setting and there is currently insufficient evidence to recommend for or against its routine use (**4**, **C**).
iii Entry into clinical trials addressing optimisation of ^{131}I therapy activity should be encouraged (**4**, **D**).
iv ^{131}I activities of 3·7–5·5 GBq are recommended for patients with known residual local disease following RRA or distant metastases (**2+**, **C**).

^{131}I therapy for pulmonary metastases—The size of pulmonary metastases influences the efficacy of ^{131}I therapy. Micronodular or miliary metastases are more likely to respond favourably to ^{131}I therapy than patients with pulmonary macronodular metastases, who rarely achieve a complete response.[44–46]

i For pulmonary metastases, repeat treatments at 6–12 month intervals are recommended provided there is continued ^{131}I uptake and evidence of ongoing benefit based on symptomatic improvement, radiological response and reduced serum Tg concentration (**4**, **D**).

^{131}I therapy for skeletal metastases

i For symptomatic solitary bone metastases consideration should be given in the first instance to complete surgical resection or high dose radiotherapy, which may be delivered using intensity modulated stereotactic radiotherapy techniques or thermal ablation depending on the site of disease (**4**, **D**).
ii ^{131}I therapy for iodine avid disease can be helpful in improving symptoms, stabilising disease and potentially improving survival[2] but rarely achieves a complete response (**2+**, **C**).

9.4. ^{131}I-refractory disease

DTC metastases frequently display reduced or no ^{131}I avidity. Interventions used in this setting aiming to increase ^{131}I avidity (retinoic acid derivatives) or ^{131}I retention (lithium) have yielded disappointing results.[47–53]

Selective mitogen-activated protein kinase (MAPK) pathway antagonists have been shown to increase the expression of the sodium-iodide symporter and uptake of iodine in mouse models. Treatment with Selumetinib, a MEK inhibitor, has demonstrated improved ^{131}I avidity in a small study[54] but phase 3 data is required. Clinical trials of Tyrosine Kinase Inhibitors in progressive, iodine refractory thyroid cancer are under way and will become available in the near future. Targeted therapies for DTC are further discussed in Chapter 12.

i The management of progressive, ^{131}I-refractory disease is largely limited to supportive care, though targeted therapies may also have a role (Chapter 12) (**4**, **D**).
ii Entry into clinical trials is encouraged (**4**, **D**).

9.5. Short-term and long-term side effects of RRA and ^{131}I therapy

If THW is the preparation method prior to ^{131}I then the main side effect is transient hypothyroidism. This is avoided in patients receiving rhTSH.

Possible early adverse events following ^{131}I.

- Dysgeusia and sialadenitis[55]
- Nausea
- Neck discomfort and swelling within a few days of ^{131}I may occur (more common when a large thyroid remnant is present)
- Radiation cystitis, radiation gastritis, bleeding and oedema in metastases are all extremely rare[56–58]

Possible late adverse events following ^{131}I.

- Xerostomia and dysgeusia
- Sialadenitis and lacrimal gland dysfunction may occur (nasolacrimal duct obstruction is very rare)
- Lifetime incidence of leukaemia and second cancers is low,[64] affecting around 0·5% of patients.[59–63] Only one of three cohort studies showed an increased but non-significant risk of leukaemia (relative risk about 2). The risk of leukaemia increases with escalating cumulative activity (greater than 18·5 GBq) and with use of additional external beam radiotherapy. Patients who have received a high cumulative ^{131}I activity may also be more likely to develop second solid malignancies (e.g. the bladder, colorectal, breast and salivary glands).[64,65]
- Radiation fibrosis can occur in patients who have had diffuse pulmonary metastatic disease and have received repeated doses of ^{131}I.[66,67]

Management of acute side-effects of ^{131}I.

i Nausea can be minimised by prescription of antiemetics (**4**, **D**).
ii Simple analgesics for neck discomfort should be tried initially. A short course of corticosteroids is recommended in severe cases (**4**, **D**).
iii For patients with known metastatic disease, especially bone and lung metastases, consideration should be given to commencing a short course of corticosteroids to minimise peritumoral oedema and an increase in local symptoms, e.g. bone pain and dyspnoea (**4 D**).
iv If the patient is to receive rhTSH then starting the corticosteroids prior to the injections is advisable (**4**, **D**).
v The total cumulative activity should be kept as low as possible (**4**, **D**).
vi Monitoring of lung function for any sign of a restrictive functional deficit is recommended in patients with lung metastases when repeated ^{131}I therapies are planned (**4**, **D**).
vii Acute symptoms of dyspnoea and cough can be reduced with prophylactic corticosteroids (**4**, **D**).

Pregnancy and Fertility—See chapter 14 'Thyroid cancer in pregnancy'.

9.6. Outpatient administration of ^{131}I for RRA or therapy

Most patients require treatment as inpatients. In selected cases outpatient treatment can be administered safely, may improve the patient experience and reduce cost. Patients must be able and willing to comply with safety procedures. The exposure dose that is considered acceptable for the safety of the general public, resulting from a patient's treatment, has been reduced in Europe after revised recommendations from the International Commission on Radiological Protection (ICRP). The annual public dose limit is 1 mSv, although adult members of the patient's family are allowed to receive higher doses, provided that the average over 5 consecutive years does not exceed 1 mSv/y.[68] A model for calculating the maximum dose of ^{131}I that may be dispensed to an outpatient has been developed.[69]

i Outpatient ^{131}I for RRA or therapy may be considered in selected patients (**4**, **D**).
ii Local protocols and procedures for safe outpatient ^{131}I for RRA or therapy must be agreed between Nuclear Medicine and the clinical team and implemented (**4**, **D**).

9.7. Aftercare following RRA and ^{131}I therapy

i After admission for RRA, local procedures should be followed and the patient discharged only after a medical physics assessment (**4**, **D**).
ii Written radiation protection advice about restricting the extent of contact between the patient and others should be handed to the patient before discharge.
Good Practice Point ☑
iii Separate restrictions should be provided for contact with adults, children, pregnant and potentially pregnant women (**4**, **D**).
iv If rhTSH is given prior to ^{131}I, thyroxine should be continued during admission (**1++**, **A**).
v If the patient undergoes THW, levothyroxine should be restarted when the patient is discharged following their ^{131}I treatment (**4**, **D**).
Key recommendation
vi A post-ablation scan should be performed after ^{131}I when residual activity levels permit satisfactory imaging (usually 2–10 days) (**2++**, **B**).
Key recommendation
vii Single-photon emission computed tomography (SPECT)-CT imaging in addition to planar imaging is helpful to localise the anatomical site of ^{131}I uptake accurately.[81] Precise localisation has been shown to alter subsequent management in 21–24% of patients, and should be considered[70,71] (**2++**, **B**).
viii Patients should be reviewed in the out patient clinic following ^{131}I treatment to discuss scan results, for clinical assessment, to adjust TSH suppressive dose of levothyroxine, and to make arrangements for follow-up Tg measurement and assessment of response by US scanning (**4**, **D**).

9.8. Assessment of RRA success

Historically in the UK, RRA success has been assessed using a combination of diagnostic ^{131}I whole body scan (WBS) with stimulated Tg assessment. Evidence over recent years has accumulated in favour of stimulated Tg (using a reliable assay, and in the absence of assay interference) (Appendix 1)[72–75] and specialised neck US[76] (Chapter 4) as a robust means to assess the success of RRA without a need for diagnostic ^{131}I WBS.

TSH stimulation can be achieved either by thyroid hormone withdrawal (THW) or by injections of rhTSH while the patient remains on suppressive thyroxine therapy.[77] The use of rhTSH is associated with better quality of life and has been shown to be cost effective[78–80] compared to THW.

i A stimulated Tg and neck US should be performed in preference to a diagnostic ^{131}I WBS between 9 and 12 months from RRA (**2+**, **C**). **Key recommendation**
ii An alternative method to stimulated Tg is the use of a sensitive method for measuring serum Tg on levothyroxine treatment for selected patients (see Chapter 11.6) (**4**, **D**).
iii rhTSH is the method of choice for Tg stimulation (**1+**, **B**).
iv The protocol for rhTSH administration or THW is the same as described in section 9·2.
v Stimulated Tg should be measured on day 5 following the first injection of rhTSH (**2++**, **B**).
vi If THW is used to assess stimulated Tg, a serum TSH concentration >30 mU/L should be achieved (**4**, **D**).
vii Neck US should assess the thyroid bed for residual thyroid tissue as well as assessing the cervical lymph nodes for signs of metastatic disease. US guided fine-needle aspiration cytology (FNAC) should be carried out when metastatic disease is suspected (**4**, **D**).

For interpretation of serum Tg, see Chapter 11.6.

Diagnostic ^{131}I or ^{123}I WBS. Only a minority of patients will require this assessment. The addition of SPECT-CT allows precise anatomical localisation of any iodine uptake demonstrated.[81]

i The principal indications for a diagnostic WBS after RRA, is in cases where measurement of serum Tg is unreliable, and where ^{131}I uptake was visualised beyond the thyroid bed and neck in the post-ablation scan (**4**, **D**).
Key recommendation
ii The ARSAC dose reference limit for ^{131}I WBS is 400 MBq[82] although many centres administer lower activities to avoid the risk of thyroid stunning in patients who might proceed to subsequent ^{131}I therapy.[83] ^{123}I WBS is a useful alternative, delivering superior image quality, lower whole body radiation dose and lower risk of stunning.[84,85] The dose reference limit is 400 MBq. Preparation for this diagnostic investigation is

the same as for RRA with TSH elevation and consideration of a low iodine diet[86] (**2+**, **C**).

iii Patients undergoing THW should have serum TSH and Tg measured before the tracer dose of ^{131}I is administered (**4**, **D**).

iv Patients receiving rhTSH should have serum Tg measured on day 5 after first injection (the same day as the scan) (**2++**, **B**).

v Patients who have undergone THW should restart levothyroxine after the scan has been reviewed and a decision made on whether additional ^{131}I treatment is required. This decision should be made as soon as the images are available and no later than a week from the scan.

Good Practice Point ☑

Dynamic Risk Stratification. Dynamic risk stratification is described and defined in Chapter 2.3. Dynamic risk stratification provides an assessment of the risk of recurrence in patients treated with total or near-total thyroidectomy with R0 resection and RRA and who have been re-evaluated after RRA with a stimulated serum Tg and US of the neck.[21,87–90] Dynamic Risk Stratification facilitates follow up, as the majority of patients will have achieved an excellent response and TSH suppression can be relaxed (Chapter 11.5), annual thyroglobulin assessment can be carried out without stimulation and follow up intervals can be extended.

i Patients treated with total thyroidectomy and RRA should undergone Dynamic Risk stratification (**3**, **D**).

Key recommendation

ii Patients should be stratified into three categories: (a) excellent response, (b) indeterminate response, (c) incomplete response (Table 2.3) (**3**, **D**).

iii Patients with an incomplete response based on evidence of residual thyroid tissue should be considered for further ^{131}I therapy once any surgically resectable disease has been excluded (**3**, **D**).

iv Patients with an incomplete response based on a stimulated Tg ≥10 mcg/l or rising Tg value and normal neck US should be assessed with cross sectional imaging or^{18}Fluoro-deoxyglucose PET-CT (Chapter 12.6). If imaging is negative ^{131}I therapy should be considered (**2++**, **B**).

v Patients with an indeterminate response need to be kept under observation with serial Tg assessments and intermittent imaging to ensure no evidence of a rising Tg concentration or progressive radiological changes indicative of persistent or progressive disease (**2++**, **B**).

vi Patients with excellent response should be considered for relaxation of TSH suppression and increase in the interval of follow-up (Chapter 11) (**3**, **D**).

References

1 Mazzaferri, E.L. & Jhiang, S.M. (1994) Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *American Journal of Medicine*, **97**, 418–428.

2 Yamashita, H., Noguchi, S., Murakami, N. *et al.* (1997) Extracapsular invasion of lymph node metastasis is an indicator of distant metastasis and poor prognosis in patients with thyroid papillary carcinoma. *Cancer*, **80**, 2268–2272.

3 Sawka, A.M., Thephamongkhol, K., Brouwers, M. *et al.* (2004) A systematic review and meta-analysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. *Journal of Clinical Endocrinology and Metabolism*, **89**, 3668–3676.

4 Haugen, B.R. (2004) Patients with differentiated thyroid carcinoma benefit from radioiodine remnant ablation. *Journal of Clinical Endocrinology and Metabolism*, **89**, 3665–3667.

5 Hackshaw, A., Harmer, C., Mallick, U. *et al.* (2007) 131I activity for remnant ablation in patients with differentiated thyroid cancer: a systematic review. *Journal of Clinical Endocrinology and Metabolism*, **92**, 28–38.

6 Mazzaferri, E.L. (1999) An overview of the management of papillary and follicular thyroid carcinoma. *Thyroid*, **9**, 421–427.

7 Reiners, C. & Farahati, J. (1999) I131 therapy of thyroid cancer patients. *Quarterly Journal of Nuclear Medicine*, **43**, 324–335.

8 Iyer, N.G., Morris, L.G., Tuttle, R.M. *et al.* (2011) Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. *Cancer*, **117**, 4439–4446.

9 Yamashita, H., Noguchi, S., Murakami, N. *et al.* (1997) Extracapsular invasion of lymph node metastasis is an indicator of distant metastasis and poor prognosis in patients with thyroid papillary carcinoma. *Cancer*, **80**, 2268–2272.

10 Cooper, D.S., Doherty, G.M., Haugen, B.R. *et al.* (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*, **19**, 1167–1214.

11 Available from: http://www.ipem.ac.uk (accessed 12 June 2014). 3Ccontains%3E+www.ipem.org.uk 102 Park HM, Park YA, Jhow XH. Detection of thyroid remnant/met

12 Sohn, S.Y., Choi, J.Y., Jang, H.W. *et al.* (2013) Association between excessive urinary iodine excretion and failure of radioactive iodine thyroid ablation in patients with papillary thyroid cancer. *Thyroid*, **23**, 741–747.

13 Sawka, A.M., Ibrahim-Zada, I., Galacgac, P. *et al.* (2010) Dietary iodine restriction in preparation for radioactive iodine treatment or scanning in well-differentiated thyroid cancer: a systematic review. *Thyroid*, **20**, 1129–1138.

14 Pluijmen, M.J., Eustatia-Rutten, C., Goslings, B.M. *et al.* (2003) Effects of low-iodide diet on postsurgical radioiodide ablation therapy in patients with differentiated thyroid carcinoma. *Clinical Endocrinology*, **58**, 428–435.

15 Lakshmanan, M., Schaffer, A., Robbins, J. *et al.* (1988) A simplified low iodine diet in I-131 scanning and therapy of thyroid cancer. *Clinical Nuclear Medicine*, **13**, 866–868.

16 www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_128166

17 Padovani, R.P., Kasamatsu, T.S., Nakabashi, C.C. *et al.* (2012) One month is sufficient for urinary iodine to return to its baseline value after the use of water-soluble iodinated contrast agents in post-thyroidectomy patients requiring radioiodine therapy. *Thyroid*, **22**, 926–930.

18 http://www.rcplondon.ac.uk/sites/default/files/documents/radioiodine-management-benign-thyroid-disease.pdf

19 Mallick, U., Harmer, C., Yap, B. *et al.* (2012) Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *New England Journal of Medicine*, **366**, 1674–1685.

20 Taïeb, D., Sebag, F., Farman-Ara, B. *et al.* (2010) Iodine biokinetics and radioiodine exposure after recombinant human thyrotropin-assisted remnant ablation in comparison with thyroid hormone withdrawal. *Journal of Clinical Endocrinology and Metabolism*, **95**, 3283–3290.
21 Lee, J., Yun, M.J., Nam, K.H. *et al.* (2010) Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. *Thyroid*, **20**, 173–179.
22 Borget, I., Corone, C., Nocaudie, M. *et al.* (2007) Sick leave for follow-up control in thyroid cancer patients: comparison between stimulation with Thyrogen and thyroid hormone withdrawal. *European Journal of Endocrinology*, **156**, 531–538.
23 Thyroid Carcinoma Task Force (2001) AACE/AAES Medical/Surgical Guidelines for Clinical Practice: Management of Thyroid Carcinoma. American Association of Clinical Endocrinologists, Jacksonville, FL. Available from: https://www.aace.com/files/thyroid-carcinoma.pdf (accessed 12 June 2014).
24 Rosário, P.W., Borges, M.A. & Purisch, S. (2008) Preparation with recombinant human thyroid-stimulating hormone for thyroid remnant ablation with ^{131}I is associated with lowered radiotoxicity. *Journal of Nuclear Medicine*, **49**, 1776–1782.
25 Ma, C., Xie, J., Liu, W. *et al.* (2010) Recombinant human thyrotropin (rhTSH) aided radioiodine treatment for residual or metastatic differentiated thyroid cancer. *Cochrane Database Systematic Review*, **11**, CD008302.
26 Reiners, C., Lassmann, M. & Luster, M. (2012) Recombinant human thyrotropin: safety and quality of life evaluation. *Journal of Endocrinological Investigation*, **35**(6 Suppl.), 30–35.
27 Sabra, M.M. & Tuttle, R.M. (2013) Recombinant human thyroid-stimulating hormone to stimulate 131-I uptake for remnant ablation and adjuvant therapy. *Endocrine Practice*, **19**, 149–156.
28 Klubo-Gwiezdzinska, J., Burman, K.D., Van Nostrand, D. *et al.* (2013) Potential use of recombinant human thyrotropin in the treatment of distant metastases in patients with differentiated thyroid cancer. *Endocrine Practice*, **19**, 139–148.
29 Robbins, R.J., Driedger, A. & Magner, J. (2006) Recombinant human thyrotropin-assisted radioiodine therapy for patients with metastatic thyroid cancer who could not elevate endogenous thyrotropin or be withdrawn from thyroxine. *Thyroid*, **16**, 1121–1130.
30 Huang, W. & Molitch, M.E. (2012) Evaluation and management of galactorrhea. *American Family Physician*, **85**, 1073–1080.
31 Bal, C.S., Kumar, A. & Pant, G.S. (2004) Radioiodine dose for remnant ablation in differentiated thyroid carcinoma: a randomized clinical trial in 509 patients. *Journal of Clinical Endocrinology and Metabolism*, **89**, 1666–1673.
32 Vini, L. & Harmer, C. (2000) Radioiodine treatment for differentiated thyroid cancer. *Journal of Clinical Oncology*, **12**, 365–372.
33 Schlumberger, M., Catargi, B., Borget, I. *et al.* (2012) Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *New England Journal of Medicine*, **366**, 1663–1673.
34 Cheng, W., Ma, C., Fu, H. *et al.* (2013) Low- or high-dose radioiodine remnant ablation for differentiated thyroid carcinoma: a meta-analysis. *Journal of Clinical Endocrinology and Metabolism*, **98**, 1353–1360.
35 Mazzaferri, E.L. & Jhiang, S.M. (1994) Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *American Journal of Medicine*, **97**, 418–428.
36 Cooper, D.S., Doherty, G.M., Haugen, B.R. *et al.* (2006) Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*, **16**, 109–142.
37 Pacini, F., Schlumberger, M., Dralle, H. *et al.* (2006) European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *European Journal of Endocrinology*, **154**, 787–803.
38 Harmer, C.L. & McCready, V.R. (1996) Thyroid cancer: differentiated carcinoma. *Cancer Treatment Reviews*, **22**, 161–177.
39 Taylor, T., Specker, B., Robbins, J. *et al.* (1998) Outcome after treatment of high risk papillary and non-Hurthle-cell follicular thyroid carcinoma. *Annals of Internal Medicine*, **129**, 622–627.
40 Kebebew, E. & Clark, O.H. (2000) Differentiated thyroid cancer 'complete' rational approach. *World Journal of Surgery*, **24**, 942–951.
41 Samuel, A.M., Rajashekharrao, B. & Shah, D.H. (1998) Pulmonary metastases in children and adolescents with well differentiated thyroid cancer. *Journal of Nuclear Medicine*, **39**, 1531–1536.
42 Bianchi, L., Baroli, A., Lomuscio, G. *et al.* (2012) Dosimetry in the therapy of metastatic differentiated thyroid cancer administering high 131I activity: the experience of Busto Arsizio Hospital (Italy). *The Quarterly Journal of Nuclear Medicine and Molecular Imaging*, **56**, 515–521.
43 Pettinato, C., Monari, F., Nanni, C. *et al.* (2012) Usefulness of 124I PET/CT imaging to predict absorbed doses in patients affected by metastatic thyroid cancer and treated with 131I. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging*, **56**, 509–514.
44 Schlumberger, M., Challeton, C. & De Vathaire, F. (1996) Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma. *Journal of Nuclear Medicine*, **37**, 598–605.
45 Hindie, E., Melliere, D., Lange, F. *et al.* (2003) Functioning pulmonary metastases of thyroid cancer: does 131-I influence the prognosis? *European Journal of Nuclear Medicine*, **30**, 974–981.
46 Brown, A.P., Greening, W.P., McCready, V.R. *et al.* (1984) 131-I treatment of metastatic thyroid carcinoma: the Royal Marsden hospital experience. *British Journal of Radiology*, **57**, 323–327.
47 Simon, D., Kohrle, J., Schmutzler, C. *et al.* (1996) Redifferentiation therapy of differentiated thyroid carcinoma with retinoic acid: basics and first clinical results. *Experimental and Clinical Endocrinology and Diabetes*, **104**(Suppl. 4), 13–15.
48 Simon, D., Koehrle, J., Reiners, C. *et al.* (1998) Redifferentiation therapy with retinoids: therapeutic option for advanced follicular and papillary thyroid carcinoma. *World Journal of Surgery*, **22**, 569–574.
49 Simon, D., Korber, C., Krausch, M. *et al.* (2002) Clinical impact of retinoids in redifferentiation therapy of advanced thyroid cancer: final results of a pilot study. *European Journal of Nuclear Medicine and Molecular Imaging*, **29**, 775–782.
50 Coelho, S.M., Corbo, R., Buescu, A. *et al.* (2004) Retinoic acid in patients with radioiodine non-responsive thyroid carcinoma. *Journal of Endocrinological Investigation*, **27**, 334–339.
51 Short, S.C., Suovuori, A., Cook, G. *et al.* (2004) A phase II study using retinoids as redifferentiation agents to increase iodine uptake in metastatic thyroid cancer. *Clinical Oncology (Royal College of Radiologist)*, **16**, 569–574.
52 Liu, Y.Y., Stokkel, M.P., Pereira, A.M. *et al.* (2006) Bexarotene increases uptake of radioiodide in metastases of differentiated

thyroid carcinoma. *European Journal of Endocrinology*, **154**, 525–531.
53 Fernández, C.A., Puig-Domingo, M., Lomeña, F. *et al.* (2009) Effectiveness of retinoic acid treatment for redifferentiation of thyroid cancer in relation to recovery of radioiodine uptake. *Journal of Endocrinological Investigation*, **32**, 228–233.
54 Ho, A.L., Grewal, R.K., Leboeuf, R. *et al.* (2013) Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *New England Journal of Medicine*, **368**, 623–632.
55 Hyer, S., Kong, A., Pratt, B. *et al.* (2007) Salivary gland toxicity after radioiodine therapy for thyroid cancer. *Clinical Oncology (Royal College of Radiologists (Great Britain))*, **19**, 83–86.
56 Maxon, H.R. & Smith, H.S. (1990) Radioiodine-131 in the diagnosis and treatment of metastatic well differentiated thyroid cancer. *Endocrinology and Metabolism Clinics of North America*, **19**, 685–718.
57 Vini, L. & Harmer, C. (2000) Radioiodine treatment for differentiated thyroid cancer. *Journal of Clinical Oncology*, **12**, 365–372.
58 Reiners, C. & Farahati, J. (1999) 131I therapy of thyroid cancer patients. *Quarterly Journal of Nuclear Medicine*, **43**, 324–335.
59 Schroeder, T. (2012) Therapy-related myeloid neoplasms following treatment with radioiodine. *Haematologica*, **97**, 206–212.
60 Sawka, A.M., Thabane, L., Parlea, L. *et al.* (2009) Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. *Thyroid*, **19**, 451–457.
61 Schlumberger, M. & Pacini, F. (1997) Hazards of medical use of iodine 131. In: Thyroid Tumours. Nucleon, Paris, 223–235.
62 Simpson, W.J., Panzarella, T., Carruthers, J.S. *et al.* (1988) Papillary and follicular thyroid cancer. Impact of treatment in 1578 patients. *International Journal of Radiation Oncology Biology Physics*, **14**, 1063–1075.
63 de Vathaire, F., Schlumberger, M., Delisle, M.J. *et al.* (1997) Leukaemia and cancers following iodine-131 administration for thyroid cancer. *British Journal of Cancer*, **75**, 734–739.
64 Rubino, C., de Vathaire, F., Dottorini, M.E. *et al.* (2003) Second primary malignancies in thyroid cancer patients. *British Journal of Cancer*, **89**, 1638–1644.
65 Sandeep, T.C., Strachan, M.W., Reynolds, R.M. *et al.* (2006) Second primary cancers in thyroid cancer patients: a multinational record linkage study. *Journal of Clinical Endocrinology and Metabolism*, **91**, 1819–1825.
66 Brown, A.P., Greening, W.P., McCready, V.R. *et al.* (1984) Radioiodine treatment of metastatic thyroid carcinoma: the Royal Marsden Hospital experience. *British Journal of Radiology*, **57**, 323–327.
67 Maheshwari, Y.K., Hill Jr, C.S., Haynie, T.P. 3rd *et al.* (1981) ^{131}I therapy in differentiated thyroid carcinoma: M.D. Anderson Hospital experience. *Cancer*, **47**:664–671.
68 de Klerk, J.M.H. (2000) 131I Therapy: inpatient or Outpatient? *Journal of Nuclear Medicine*, **41**, 1876–1878.
69 Coover, L.R., Silberstein, E.B., Kuhn, P.J. *et al.* (2000) Therapeutic 131I in outpatients: a simplified method conforming to the Code of Federal Regulations, title 10, part 35.75. *Journal of Nuclear Medicine*, **41**, 1868–1875.
70 Spanu, F., Solinas, M.E., Chessa, F. *et al.* (2009) I-131 SPECT CT in the follow up of differentiated thyroid cancer: incremental value versus planar imaging. *Journal of Nuclear Medicine*, **50**, 184–190.
71 Kohlfuerst, S., Igerc, I., Lobnig, M. *et al.* (2009) Post therapeutic I-131 SPECT CT offers high diagnostic accuracy when the findings on conventional planar imaging are inconclusive and allows a tailored patient treatment regimen. *European Journal of Nuclear Medicine and Molecular Imaging*, **36**, 886–893.
72 Pacini, F., Schlumberger, M., Dralle, H. *et al.* (2006) European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *European Journal of Endocrinology*, **154**, 787–803.
73 Schlumberger, M., Berg, G., Cohen, O. *et al.* (2004) Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. *European Journal of Endocrinology*, **150**, 105–112.
74 Mazzaferri, E.L., Robbins, R.J., Spencer, C.A. *et al.* (2003) A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism*, **88**, 1433–1441.
75 Sherman, S.I. (2013) The role of recombinant human thyrotropin for diagnostic monitoring of patients with differentiated thyroid cancer. *Endocrine Practice*, **19**, 157–161.
76 Torlontano, M., Crocetti, U., Augello, G. *et al.* (2006) Comparative evaluation of recombinant human thyrotropin-stimulated thyroglobulin levels, 131I whole-body scintigraphy, and neck ultrasonography in the follow-up of patients with papillary thyroid microcarcinoma who have not undergone radioiodine therapy. *Journal of Clinical Endocrinology and Metabolism*, **91**, 60–63.
77 Haugen, B.R., Pacini, F., Reiners, C. *et al.* (1999) A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *Journal of Clinical Endocrinology and Metabolism*, **84**, 3877–3885.
78 Lee, J., Yun, M.J., Nam, K.H. *et al.* (2010) Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. *Thyroid*, **20**, 173–179.
79 Borget, I., Corone, C., Nocaudie, M. *et al.* (2007) Sick leave for follow-up control in thyroid cancer patients: comparison between stimulation with Thyrogen and thyroid hormone withdrawal. *European Journal of Endocrinology*, **156**, 531–538.
80 Mernagh, P., Suebwongpat, A., Silverberg, J. *et al.* (2010) Cost-effectiveness of using recombinant human thyroid-stimulating hormone before radioiodine ablation for thyroid cancer: the Canadian perspective. *Value Health*, **13**, 180–187.
81 Barwick, T.D., Dhawan, R.T. & Lewington, V. (2012) Role of SPECT/CT in differentiated thyroid cancer. *Nuclear Medicine Communications*, **33**, 787–798.
82 ARSAC Notes for Guidance. Health Protection Agency for the Administration of Radioacrive Substances Committee 2006 (2011 revision).
83 Leger, F.A., Izembart, M., Dagousset, F. *et al.* (1998) Decreased uptake of therapeutic doses of I-131 after 185 MBq Iodine-131 diagnostic imaging for thyroid remnants in differentiated thyroid carcinoma. *European Journal of Nuclear Medicine*, **25**, 242–246.
84 Hilditch, T.E., Dempsey, M.F., Bolster, A.A. *et al.* (2002) Self stunning in thyroid ablation: evidence from comparative studies of diagnostic I-131 and I-123. *European Journal of Nuclear Medicine and Molecular Imaging*, **29**, 783–788.
85 Urhan, M., Dadparvar, S., Mavi, A. *et al.* (2007) Iodine-123 as a diagnostic imaging agent in differentiated thyroid carcinoma: a

comparison with Iodine-131 post treatment scanning and serum thyroglobulin measurement. *European Journal of Nuclear Medicine and Molecular Imaging*, **34**, 1012–1017.

86 Sawka, A.M., Ibrahim-Zada, I., Galacgac, P. *et al.* (2010) Dietary iodine restriction in preparation for radioactive iodine treatment or scanning in differentiated thyroid cancer. *Thyroid*, **20**, 1129–1138.

87 Castagna, M.G., Maino, F., Cipri, C. *et al.* (2011) Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients. *European Journal of Endocrinology*, **165**, 441–446.

88 Vaisman, F., Shaha, A., Fish, S. *et al.* (2011) Initial therapy with either thyroid lobectomy or total thyroidectomy without radioactive iodine remnant ablation is associated with very low rates of structural disease recurrence in properly selected patients with differentiated thyroid cancer. *Clinical Endocrinology*, **75**, 112–119.

89 Vaisman, F., Tala, H., Grewal, R. *et al.* (2011) In differentiated thyroid cancer, an incomplete structural response to therapy is associated with significantly worse clinical outcomes than only an incomplete thyroglobulin response. *Thyroid*, **21**, 1317–1322.

90 Pitoia, F., Bueno, F., Urciuoli, C. *et al.* (2013) Outcomes of patients with differentiated thyroid cancer risk-stratified according to the American Thyroid Association and Latin American Thyroid Society risk of recurrence classification systems. *Thyroid*, **23**, 1401–1407.

CHAPTER 10

10 External beam radiotherapy for differentiated thyroid cancer

10.1. Adjuvant treatment

The evidence for efficacy of external beam radiotherapy (EBRT) in differentiated thyroid cancer (DTC) is mixed. The data sets that have been published are subject to the inherent bias of retrospective series with mixed patient populations and histological subtypes over long periods of time during which there were variations in therapy and changes in staging. In addition, the primary end points for studies evaluating the role of EBRT in thyroid cancer are difficult to define and are variable within the published series.

A number of retrospective series have shown a statistically significant benefit for EBRT in terms of local disease control.[1–7] Only three studies evaluating the effect of EBRT on local recurrence rates involved patients in whom ^{131}I ablative therapy was routinely used, and are consequently the most informative.[2–4]

i The indications for consideration of adjuvant EBRT are for patients with a high risk of recurrence/progression with: (a) gross evidence of local tumour invasion at surgery with significant macroscopic residual disease, or (b) residual or recurrent tumour that fails to concentrate radioiodine, i.e. loco-regional disease where further surgery or radioiodine is ineffective or impractical (**2−**, **D**).

Key recommendation

ii The indications for primary management with EBRT are rare and fall into the palliative setting where a specific symptom is to be addressed with no intent to cure (**4**, **C**).

10.2. EBRT dose, fractionation and target volume

The absence of randomised data and the evolution of radiotherapy techniques over the past 40 years make the interpretation of dose–response effects problematic.

Data available appears to show a dose response and doses >50 Gy correlate with greater local control.[8,9] A typical postoperative dose is 60 Gy in 30 daily fractions. Higher doses could be given to small volume sites of macroscopic residuum. Acute toxicity resulting from Intensity Modulated Radiotherapy (IMRT) has been shown to be acceptable and equivalent to conventional techniques.[10,11] Longer term follow-up and larger series are awaited before conclusions can be drawn on late toxicity. There is also a theoretical concern in delivering EBRT in close temporal proximity to ^{131}I, of augmenting radiation-related toxicity. This is of particular concern in patients with residual macroscopic disease invading local structures such as the trachea, who will probably receive both EBRT and ^{131}I. This question remains unanswered.

i The target volume should include the thyroid bed (usually hyoid to sternal notch, both carotid sheaths, the front of the vertebral body, including in particular the tracheo-oesophageal groove) and draining lymph nodes (perithyroidal lymph nodes, paratracheal, pretracheal, superior mediastinum and cervical lymph nodes) in papillary and oncocytic follicular (Hürthle cell) cancers[12] (**4**, **D**). Draining lymph nodes do not need to be irradiated in non-oncocytic follicular thyroid cancer unless there is confirmed nodal involvement.

ii IMRT is the delivery technique of choice as it permits treatment of concave structures, thus minimising the dose to the spinal cord and parotid glands and significantly improving the target volume coverage all in a single phase[13,14] (**1**, **A**).

iii If IMRT is not available a conventional 2-phase CT conformal plan should be employed. In the first phase, 44 Gy is delivered in 22 fractions with the remaining 16 Gy in eight fractions in the second phase anterior to spinal cord[15] (**4**, **D**).

iv The timing of EBRT in relation to ^{131}I remnant ablation (RRA) and ^{131}I therapy is not well evidenced. EBRT has been used postoperatively, following RRA to obviate concerns of possible stunning effect of EBRT on thyroid cells, which may influence the efficacy of subsequent ^{131}I but there is insufficient evidence to recommend an optimal sequencing (**4**, **D**).

v If residual disease presents a threat to a critical structure such as the airway, EBRT should be considered prior to ^{131}I to lessen the risk of complications due to RAI induced tumour oedema (**4**, **D**).

10.3. EBRT in the palliative setting

There are several clinical scenarios where EBRT can provide effective palliation, including bone metastases, spinal cord compression, bleeding, brain metastases and painful masses that are no longer iodine avid. There are some circumstances in which EBRT may be used in preference to ^{131}I, even in patients with multifocal iodine-avid disease, such as for spinal metastases with encroachment on the thecal sac or orbital metastases where the use of ^{131}I may result in tumour flare and exacerbation of symptoms with deleterious neurological consequences. There is little data in the literature to guide decisions on the timing, dose or fractionation of EBRT in the palliation of thyroid cancer. There have been several large randomized trials and systematic reviews (including a Cochrane review)[16] that have included patients with thyroid cancer evaluating the efficacy of various dose/fractionation schedules on outcome in the palliation of bone metastases. Single fraction regimens were shown to be at least as effective as fractionated regimens in all prospective randomised trials for

different bone-seeking cancers.[17] Patients with breast, prostate, kidney and lung tumours showed improved pain relief with radiation doses above 40 Gy compared with below 40 Gy. However, this effect was not seen in patients with thyroid cancer associated bone metastases.

i A single fraction or a short course (20 Gy in five fractions over one week) is recommended for palliation, which can subsequently be repeated if required (**1+**, **A**).
ii In patients with good performance status and limited metastatic disease, higher palliative doses (>40 Gy) may be considered (**4**, **D**).
iii For management of rapidly progressive neck masses 30 Gy in 10 fractions over 2 weeks can be safely prescribed with a simple anterior/posterior beam arrangement to enable rapid start of treatment (**4**, **D**).

EBRT for MTC and ATC is described in chapters 17 and 18 respectively.

References

1 Esik, O., Nemeth, G. & Eller, J. (1994) Prophylactic external irradiation in differentiated thyroid cancer: a retrospective study over a 30-year observation period. *Oncology*, **51**, 372–379.
2 Farahati, J., Reiners, C., Stuschke, M. *et al.* (1996) Differentiated thyroid cancer. Impact of adjuvant external radiotherapy in patients with perithyroidal tumor infiltration (stage pT4). *Cancer*, **77**, 172–180.
3 Chow, S.M., Law, S.C., Mendenhall, W.M. *et al.* (2002) Papillary thyroid carcinoma: prognostic factors and the role of radioiodine and external radiotherapy. *International Journal of Radiation Oncology Biology Physics*, **52**, 784–795.
4 Kim, T.H., Yang, D.S., Jung, K.Y. *et al.* (2003) Value of external irradiation for locally advanced papillary thyroid cancer. *International Journal of Radiation Oncology Biology Physics*, **55**, 1006–1012.
5 Tsang, R.W., Brierley, J.D., Simpson, W.J. *et al.* (1998) The effects of surgery, radioiodine, and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. *Cancer*, **82**, 375–388.
6 Simpson, W.J., Panzarella, T., Carruthers, J.S. *et al.* (1988) Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. *International Journal of Radiation Oncology Biology Physics*, **14**, 1063–1075.
7 Sia, M.A., Tsang, R.W., Panzarella, T. *et al.* (2010) Differentiated thyroid cancer with extrathyroidal extension: Prognosis and the role of external beam radiotherapy. *Journal of Thyroid Research*, 183461. doi: 10.4061/2010/183461.
8 Ford, D., Giridharan, S., McConkey, C. *et al.* (2003) External beam radiotherapy in the management of differentiated thyroid cancer. *Clinical oncology (Royal College of Radiologists (Great Britain))*, **15**, 337–341.
9 Tubiana, M., Haddad, E., Schlumberger, M. *et al.* (1985) External radiotherapy in thyroid cancers. *Cancer*, **55**(9 Suppl.), 2062–2071.
10 Terezakis, S.A., Lee, K.S., Ghossein, R.A. *et al.* (2009) Role of external beam radiotherapy in patients with advanced or recurrent nonanaplastic thyroid cancer: memorial Sloan-Kettering Cancer Center experience. *International Journal of Radiation Oncology Biology Physics*, **73**, 795–801.
11 Schwartz, D.L., Lobo, M.J., Ang, K.K. *et al.* (2009) Postoperative external beam radiotherapy for differentiated thyroid cancer: outcomes and morbidity with conformal treatment. *International Journal of Radiation Oncology Biology Physics*, **74**, 1083–1091.
12 Azrif, M., Slevin, N.J., Sykes, A.J. *et al.* (2008) Patterns of relapse following radiotherapy for differentiated thyroid cancer: implication for target volume delineation. *Radiotherapy and Oncology*, **89**, 105–113.
13 Nutting, C.M., Convery, D.J., Cosgrove, V.P. *et al.* (2001) Improvements in target coverage and reduced spinal cord irradiation using intensity-modulated radiotherapy (IMRT) in patients with carcinoma of the thyroid gland. *Radiotherapy and Oncology*, **60**, 173–180.
14 Brierley, J, Rumble, RB, Warde, P *et al.* The Role of IMRT in thyroid cancers. Available from: http://www.cancercare.on.ca/toolbox/qualityguidelines/clin-program/radther/ (accessed 12 June 2014).
15 Harmer, C., Bidmead, M., Shepherd, S. *et al.* (1998) Radiotherapy planning techniques for thyroid cancer. *British Journal of Radiology*, **71**, 1069–1075.
16 Sze, W.M., Shelley, M.D., Held, I. *et al.* (2003) Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy – a systematic review of randomised trials. *Clinical Oncology*, **15**, 345–352.
17 Falkmer, U., Jarhult, J., Wersall, P. *et al.* (2003) A systematic overview of radiation therapy effects in skeletal metastases. *Acta Oncologica*, **42**, 620–633.

CHAPTER 11

11 Post-treatment follow-up of patients with differentiated thyroid cancer

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, which may include fine-needle aspiration cytology (FNAC) (**4**, **D**).

11.1. Voice dysfunction

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

i It is recommended that patients with voice change after thyroidectomy undergo laryngoscopy[1] (**2−**, **C**).
ii The patient should be referred to a specialist practitioner capable of carrying out direct and/or indirect laryngoscopy (**4**, **D**).

11.2. Management of acute post-thyroidectomy hypocalcaemia

After total thyroidectomy, 30% of patients will need calcium supplementation with or without alfacalcidol/calcitriol. By 3 months, <10% of patients will still require calcium supplementation.[2–4]

Hypoparathyroidsm is often transient and a predictor of this is an elevated (or upper normal range) serum parathyroid hormone (PTH) concentration at the time of the occurrence of hypocalcaemia.[2] Thus, the majority of patients on calcitriol/alfacalcidol/calcium supplements can have this treatment withdrawn.[5]

A decline in serum calcium concentration in the first 24 hours after surgery is predictive of the need for calcium supplementation.[6]

Detailed guidance on the management of hypocalcamia has been produced by the Society for Endocrinology.[7]

i Serum calcium should be checked on the day after surgery (or earlier if symptoms occur), and daily until the hypocalcaemia improves[8,9] (**3**, **D**).
ii If hypocalcaemia develops, calcium supplementation should be started (initial dosage: Sandocal™ 1000, 2 tablets BD or 1 tablet qds if unable to tolerate, or Adcal 3 tablets BD, or Cacit 4 tablets BD, or Calcichew Forte 2 tablets BD) (**4**, **D**).
iii When adjusted calcium is >2·1 mM, patient may be discharged with arrangements to recheck calcium within 1 week (**4**, **D**).
iv If serum calcium remains between 1·9 and 2·1 mM and the patient is asymptomatic, increase calcium supplements (Sandocal™ 1000 to three BD or equivalent) (**4**, **D**).
v If the patient remains mildly hypocalcaemic beyond 72 hours post operatively despite calcium supplementation, alfacalcidol 0·25 mcg/day or calcitriol 0·25 mcg/day should be commenced with close monitoring (**4**, **D**).
vi In severe symptomatic hypocalcaemia (adjusted calcium (<1·9 mM and/or symptomatic at any level below reference range) IV calcium gluconate should be administered, initially 10–20 ml 10% calcium gluconate in 50–100 ml of 5% dextrose IV over 10 minutes with ECG monitoring. This can be repeated until the patient is asymptomatic. It should be followed up with a calcium gluconate infusion as follows: (**4**, **D**)
    - Dilute 100 ml of 10% calcium gluconate (10 vials) in 1 litre of Normal saline or 5% dextrose and infuse at 50–100 ml/h (calcium chloride can be used as an alternative to calcium gluconate but it is more irritant to veins and should only be given via a central line)
    - Titrate the rate of infusion to achieve normocalcaemia.
    - Alfacalcidol 0·25 μg/day or calcitriol 0·25 μg/day should be commenced with close monitoring
    - The calcium infusion should continue until the serum calcium has normalized
vii In a minimally symptomatic or an asymptomatic patient with severe hypocalcaemia, oral calcium supplementation with alfacalcidol 0·25 μg/day or calcitriol 0·25 μg/day, should be considered initially as an alternative to IV calcium gluconate therapy (**4**, **D**).

11.3. Long-term management of hypoparathyroidism

i Before committing patients with post-thyroidectomy hypocalcaemia to life-long substitution therapy with alfacalcidol/calcitriol and calcium, an attempt should be made to wean them off supplements in an outpatient setting (**4**, **D**).
Key recommendation
ii Monitoring of serum calcium should be supervised in the specialist clinic, with the assistance of the GP if appropriate (**4**, **D**).
iii Supplements should be slowly and gradually reduced and serum calcium monitored every few months until withdrawn and eucalcaemia restored (**4**, **D**).
iv The combined effects of hypocalcaemia and hypothyroidism are poorly tolerated and alfacalcidol/calcitriol/calcium supple-

Table 11.1. Use and interpretation of Fracture Risk Assessment Tool (FRAX)

Background
- The risk of osteoporotic fracture is probably increased in post-menopausal women with TSH suppressed below 0·05 mIU/l for >5 years
- The WHO Fracture Risk Assessment Tool (FRAX) is an on-line application that can be used to evaluate fracture risk of individual patients in the clinic
- FRAX does not include thyrotoxicosis or TSH suppression as a specific risk factor for fracture; nevertheless:
  - 1 standard deviation fall in bone mineral density (BMD) T-score results in a 2·5–3·0 fold increased risk of hip fracture (32)
  - TSH suppressed <0·05 mIU/l is associated with a 2·5–3·0 fold increased risk of hip fracture (28–30)
  - Patients with TSH suppressed below 0·05 mIU/l for >5 years can be considered to have their measured BMD T-score reduced by 1 standard deviation for the purposes of FRAX risk assessment

Practical advice
- When completing FRAX on-line (Available from: http://www.shef.ac.uk/FRAX) the femoral neck BMD T-score should be reduced by 1 if the patient has TSH suppressed below 0·05 mU/l for >5 years
  - The 10-year probabilities of a major osteoporotic fracture and a hip fracture are calculated
  - A link to the National Osteoporosis Guideline Group (NOGG) provides advice on data interpretation and patient management, together with a graph indicating whether the patient requires (a) treatment, (b) further measurement of BMD or (c) lifestyle advice and reassurance

ment withdrawal should be avoided during periods of unstable thyroid status (**4**, **D**).

v If hypoparathyroidism is permanent, the lowest dose of supplements should be administered to maintain the serum calcium at the lower end of the normal range, while avoiding hypercalciuria (**4**, **D**).

vi Patients on long-term alfacalcidol/calcitriol treatment should be monitored for adverse effects, which include hypercalcaemia, hypercalciuria, renal impairment, nephrocalcinosis and kidney stones. Thus, serum calcium tests should be undertaken at 3 monthly intervals or more frequently until the biochemistry is stable. Estimations of urinary calcium excretion, serum calcium and creatinine and ultrasonography (US) of the kidneys, should be performed annually. The occurrence of these adverse effects should necessitate a reduction (or cessation) of the dose of alfacalcidol/calcitriol (**4**, **D**).

Key recommendation

11.4. Management of iatrogenic hypercalcaemia

i The correct treatment of hypercalcaemia occurring in a patient receiving alfacalcidol/calcitriol therapy is to stop that treatment and to ensure adequate hydration by oral or intravenous fluids. Bisphosphonate drugs should not be administered, as in the absence of PTH drive they can result in severe, prolonged, or even life-threatening hypocalcaemia. In exceptional circumstances, if bisphosphonate use is being considered specialist endocrine advice should be sought (**4**, **D**).

11.5. Suppression of serum thyroid stimulating hormone (TSH)

Supra-physiological doses of levothyroxine are used to reduce the risk of thyroid cancer recurrence.[10–12] A meta-analysis supported the efficacy of TSH suppression in preventing major adverse clinical events.[13] On physiological grounds it may be desirable to avoid complete suppression of the serum TSH below 0·01 mU/l on sensitive assays, though there is no evidence for or against this practice. Adverse effects from long-term TSH suppression include increased risk of atrial fibrillation, cardiovascular disease and death[14–16] as well as osteoporosis.[17–19]

i Patients who have not received radioiodine remnant ablation (RRA) because they fall in the 'no indication for RRA' group (Chapter 9.1), do not require TSH suppression and the serum TSH should be maintained in the low-normal range between 0.3 and 2.0 mU/l (**4**, **D**).

ii Levothyroxine should be used in preference to liothyronine for long-term suppression[20] (**2++**, **B**).

iii Following initial treatment with total thyroidectomy and radioiodine remnant ablation (RRA), and before evaluation of the patient's response to treatment after 9–12 months, TSH should be suppressed to below 0·1 mU/l in all patients (**4**, **D**).

Key recommendation

iv Following evaluation of response after 9–12 months after total thyroidectomy and RRA, the risk of thyroid cancer recurrence should be reclassified according to the criteria for Dynamic Risk Stratification (Chapter 2.3, Table 2.3). This re-stratification should be documented in the notes and the degree of TSH suppression adjusted accordingly)[11,12] (**4**, **D**).

v The need for long-term TSH suppression should be based on Dynamic Risk Stratification determined 9–12 months following total thyroidectomy and RRA[11, 13, 21–23] as follows (Chapter 2.3, Table 2.3):

- In patients with an incomplete response to treatment for thyroid cancer (as defined in Chapter 2.3) the serum TSH should be suppressed below 0·1 mU/l indefinitely in the absence of specific contra-indications[11–15,24–26] (**2+**, **C**).
- In patients who have an indeterminate response, it is recommended that the goal of TSH suppressive therapy be adjusted to maintain serum TSH concentrations between 0·1 and 0·5 mU/l for 5–10 years at

which point the need for continuing TSH suppression should be re-evaluated[11–15,21–23] (**2+**, **C**).

- In patients with an excellent response to treatment for thyroid cancer, the serum TSH should be maintained in the low-normal range between 0·3–2 mU/l[11,12,21–23,27,28] (**1+**, **A**).
- For historical patients who have not undergone Dynamic Risk Stratification, it is recommended that serum TSH should be suppressed below 0·1 mU/l for 5–10 years. This suppression can then be relaxed as appropriate, based on clinical, radiological or biochemical assessment of response (**4**, **D**).

Key recommendation

vi The dose of levothyroxine should be adjusted by 25 μg no more frequently than every 6–8 weeks (except in pregnancy, Chapter 14) until the serum TSH is within the required target range (**4**, **D**).

vii During follow-up, the degree of TSH suppression should be re-evaluated every few years to ensure the TSH target range correlates with the re-assessed risk of recurrence and death (**4**, **D**).

viii At any time the potential benefits of TSH suppression should be considered and balanced against the potential adverse effects of TSH suppression on the heart and the skeleton[29,30] (**2++**, **B**).

ix In specific at risk patient groups such as post-menopausal women, assessment of the 10-year probability of osteoporotic fragility fracture should also be performed using the WHO Fracture Risk Assessment Tool (FRAX): Available from: http://www.shef.ac.uk/FRAX[31,32] (Table 11.1) (**4**, **D**).

Key recommendation

x Patients who have undergone hemithyroidectomy only because of tumour ≤1 cm and low risk of recurrence (Table 2.2, Chapters 7 and 8), do not require TSH suppression or long-term follow-up,[33–35] other that annual thyroid function testing by their GP; replacement treatment with levothyroxine should be given to patients with overt hypothyroidism[36] (**4**, **D**).

xi Patients with low risk (Table 2.2, Chapter 7) tumours >1 to <4 cm treated with hemithyroidectomy, may have a slightly higher risk of local recurrence than patients treated with total thyroidectomy, usually detectable within 3–5 years and mostly by 8–10 years. Appropriate and timely detection and treatment of these recurrences is important in order to achieve similar overall survival to patient treated with total thyroidectomy[37,38] Low risk cases with tumour >1 to <4 cm treated with hemoithyroidectomy do not require TSH suppression, but **Personalised Decision Making** (Chapter 2.4, Table 2.4) is recommended with regards to frequency and duration of follow-up (**4**, **D**).

xii Suppressive levothyroxine therapy is best supervised by a member of the MDT, preferably by an endocrinologist, although alternative arrangements may be appropriate in low-risk cases (for definition of low risk see Chapters 2.3; for follow-up of low risk cases see Chapter 13) (**4**, **D**).

xiii The GP should be advised of the reason for TSH suppression and of the target serum TSH concentration. The need to measure serum free thyroxine (fT4) and TSH concentration should also be made clear (**4**, **D**).

11.6. Measurement of serum thyroglobulin (Tg) in long-term follow-up (see also Appendix 1)

Tg is secreted by both normal and cancerous thyroid cells. In patients who have not had a total thyroidectomy and RRA, the interpretation of serum Tg measurements is limited by the inability to differentiate between tumour and thyroid remnant, though trends over time are informative.[39,40] In the post-thyroidectomy setting, a 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. A serum Tg rising with time while on suppressive thyroxine therapy is highly suggestive of tumour recurrence or progression. Endogenous Tg antibodies (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. Serial measurement of TgAb is of value in the longer term monitoring of patients with differentiated thyroid cancer (DTC).[41] TgAb concentrations decline with successful removal of Tg antigenic stimulus (following thyroidectomy and RRA) over a median time of 3 years. De novo appearance or a rising trend in TgAb concentration is a significant risk factor for recurrent disease. Heterophile antibodies may falsely increase or decrease thyroglobulin measurement in patients with DTC.[42] The management of patients with elevated serum Tg indicative of persistent or recurrent disease is discussed in Chapter 12.

i To ensure continuity in monitoring, clinicians should use the same laboratory, Tg and TgAb assays on a long-term basis. Laboratories should not change methods without prior consultation with clinical users of the service (**4**, **D**).

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 measured[43] (**4**, **D**).

Key recommendation

iii Samples should not be collected sooner than 6 weeks post-thyroidectomy or RRA/^{131}I therapy[37, 44–47] (**2+**, **C**).

Key recommendation

iv There is normally no need to measure serum Tg more frequently than 3-monthly during routine follow-up. For low risk patients with no evidence of biochemical or structural disease an annual measurement of serum Tg while on suppressive levothyroxine treatment is adequate (**4**, **D**).

v 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.
Good Practice Point ☑

vi Patients in whom the basal Tg remains persistently detectable (i.e. while on suppressive levothyroxine therapy) or rises with subsequent assessments require further evaluation (**2++**, **B**).

vii At routine follow-up most patients should have serum Tg measured while on TSH suppression (**2++**, **B**).

viii Where the Tg result does not correlate with the clinical picture, clinicians should highlight this to the laboratory.
Good Practice Point ☑

TSH-stimulated serum Tg (sTg) measurement. The diagnostic sensitivity of serum Tg measurements is enhanced by an elevated serum TSH concentration. Tumour recurrence or progression can be diagnosed earlier by detecting a raised serum Tg after TSH stimulation than by measurement of Tg on suppressive levothyroxine therapy.

Interpretation of sTg. sTg can only be interpreted in the absence of assay interference (Appendix 1), and is most informative when patients have undergone RRA. A sTg<0·5 μg/l after rhTSH has been shown to identify patients free of disease with a 98–99·5% probability.[48,49] A sTg > 2 μg/l following rhTSH stimulation, is highly sensitive in identifying patients with persistent disease,[50–55] though the specificity is low (in one series about one third of patients with sTg> 2 μg/l had persistent disease).[56] Tg cut-off values however are highly dependent on the characteristics of the assay.

An unstimulated serum Tg <0·1 μg/l measured by a sensitive assay in the absence of TgAbs has a very high negative predictive value in selected patients (those who have been subjected to total thyroidectomy and RRA, are at low risk of recurrence and have a negative US of the neck). This strategy can be cost-effective and obviate the need for sTg assessments.[57–62] While assay technology is evolving and becoming more sophisticated, cut-off values for informing clinical decisions still need to be established for each laboratory.

i Sensitive Tg measurements without TSH stimulation can be used in selected patients (treated with total thyroidectomy and RRA, at low risk of recurrence, with a negative US of the neck) instead of sTg in order to identify those who require less intensive monitoring. However, it is recommended that laboratories establish/confirm the cut-off serum Tg values beyond which clinical decisions can be based (**4**, **D**).

ii sTg should be measured when the serum TSH is more than 30 mIU/l when thyroid hormone withdrawal (THW) is the method of stimulation (**4**, **C**).

iii In low-risk (Chapter 2.3, Table 2.2) patients who have undetectable serum Tg while on suppressive thyroxine therapy, sTg measurement alone (i.e. without a concomitant whole-body scan (WBS)) represents adequate initial follow-up, provided there is no Tg assay interference and an US of the neck is negative.[63–65] A concomitant WBS in such cases rarely adds valuable information (**2+**, **C**).

iv If serum Tg is undetectable under TSH stimulation and the US of the neck is negative, subsequent long-term follow-up by measurement of serum Tg while on levothyroxine treatment is sufficient[66–67] (**2++**, **B**).

TSH stimulation can be achieved either by THW (aiming for a serum TSH >30 mIU/l; Chapter 9.8), or by injections of rhTSH while the patient remains on suppressive levothyroxine therapy[68] (note that the target serum TSH >30 mIU/l at the time of sTg measurement does not apply when rhTSH injections are used). The use of rhTSH is associated with better quality of life and has been shown to be cost effective[69–71] compared to THW. A single undetectable sTg in the absence of assay interference is highly predictive of no future recurrence, provided the Tg can be measured reliably in low-risk patients (Chapter 2.3) who have undergone total or near-total thyroidectomy and RRA. The role of neck US in such cases is discussed in Chapter 9.7.

i rhTSH is the method of choice for thyroglobulin stimulation (**1+**, **B**).
Key recommendation

ii sTg measurements (with or without a WBS) and US of the neck should be performed 9–12 months after RRA or ^{131}I therapy (**4**, **D**).

iii sTg may remain detectable at low concentrations after RRA. 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 cases (defined in Chapter 2.3, and Table 2.2) is recommended with repeat sTg assessments at 12 month intervals (**4**, **D**).

iv In many cases, repeat assessments will reveal a gradual decline in sTg to the point of no detection; routine follow-up should then be resumed (**4**, **D**).

v Patients in whom the sTg remains persistently detectable or rises with subsequent assessments require further evaluation (**2+**, **C**).

Recommendations for the use of rhTSH-stimulated Tg in routine follow-up. TSH stimulation for measurement of sTg (or for WBS) can be achieved by thyroid hormone THW or by administration of rhTSH. rhTSH is the method of choice for sTg or WBS assessment. For the groups of patients with the following conditions, rhTSH is the only possible or safe option for diagnostic purposes[72] and for ablation or therapy:

- hypopituitarism
- severe ischaemic heart disease
- previous history of psychiatric disturbance precipitated by hypothyroidism
- advanced disease/frailty.

i 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 (**4**, **D**).

ii rhTSH (two 0·9 mg doses) should be administered by deep intramuscular injection into the buttock on days 1 and 2 and serum Tg measured on day 5 (**1++**, **A**).

iii When a Tg sample is being collected after ^{131}I administration 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.

Good Practice Point ☑

iv rhTSH should not be used if basal (unstimulated) serum Tg is elevated or the patient is expected to have ^{131}I therapy with THW (**4**, **D**).

v rhTSH should be used with care if there is known or suspected tumour close to the central nervous system. Steroid cover is recommended in such cases (**4**, **D**).

References

1 Chandrasekhar, S.S., Randolph, G.W., Seidman, M.D. *et al.* (2013) Clinical practice guideline: improving voice outcomes after thyroid surgery. *Otolaryngology - Head and Neck Surgery*, **148**(Suppl. 6), S1–37.

2 Thakker, RV. (2003) Hypocalcemia: pathogenesis, differential diagnosis and management. In: M.J. Favus ed. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolisim, 5th edn. American Society of Bone and Mineral Research, Washington, DC, 271–274

3 Hannan, F.M. & Thakker, R.V. (2013) Investigating Hypocalcaemia. *BMJ*, **9**, 346, f2213.

4 Thakker, RV (2010) Parathyroid disorders and diseases affecting calcium homeostasis. In: D Warrell, T Cox, JD Firth eds. Oxford Textbook of Medicine, 5th edn. Oxford University Press, Oxford, UK, 1851–1868.

5 Thakker, RV (2006) Hypocalcemia: pathogenesis differential diagnosis and management. In: M.J. Favus ed. ASBMR Primer 6th Edition on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. American Society of Bone and Mineral Research, Philadelphia, 213–215.

6 Chia, SH, Weisman, RA, Tieu, D *et al.* (2006) Prospective study of perioperative factors predicting hypocalcemia after thyroid and parathyroid surgery. *Archives of Otolaryngology - Head and Neck Surgery* **132**, 41–45.

7 http://www.endocrinology.org/policy/docs/13-02_EmergencyGuidance-AcuteHypocalcaemia_(inAdults).pdf

8 Szubin, L., Kacker, A., Kakani, R. *et al.* (1996) The management of post-thyroidectomy hypocalcemia. *Ear, Nose, and Throat Journal*, **75**, 612–4, 616.

9 Bentrem, D.J., Rademaker, A. & Angelos, P. (2001) Evaluation of serum calcium levels in predicting hypoparathyroidism after total/near-total thyroidectomy or parathyroidectomy. *American Surgeon*, **67**, 249–251.

10 Brabant, G. (2008) Thyrotropin suppressive therapy in thyroid carcinoma: what are the targets? *Journal of Clinical Endocrinology and Metabolism*, **93**, 1167–1169.

11 Cooper, D.S., Doherty, G.M., Haugen, B.R. *et al.* (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*, **19**, 1167–1214.

12 Jonklaas, J., Sarlis, N.J., Litofsky, D. *et al.* (2006) Outcomes of patients with differentiated thyroid carcinoma following initial therapy. *Thyroid*, **16**, 1229–1242.

13 McGriff, N.J., Csako, G., Gourgiotis, L. *et al.* (2002) Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer. *Annals of Medicine*, **34**, 554–564.

14 Collet, T.H., Gussekloo, J., Bauer, D.C. *et al.* (2012) Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Archives of Internal Medicine*, **172**, 799–809.

15 Haentjens, P., Van, M.A., Poppe, K. *et al.* (2008) Subclinical thyroid dysfunction and mortality: an estimate of relative and absolute excess all-cause mortality based on time-to-event data from cohort studies. *European Journal of Endocrinology*, **159**, 329–341.

16 Yang, L.B., Jiang, D.Q., Qi, W.B. *et al.* (2012) Subclinical hyperthyroidism and the risk of cardiovascular events and all-cause mortality: an updated meta-analysis of cohort studies. *European Journal of Endocrinology*, **167**, 75–84.

17 Lee, J.S., Buzkova, P., Fink, H.A. *et al.* (2010) Subclinical thyroid dysfunction and incident hip fracture in older adults. *Archives of Internal Medicine*, **170**, 1876–1883.

18 Murphy, E., Gluer, C.C., Reid, D.M. *et al.* (2010) Thyroid function within the upper normal range is associated with reduced bone mineral density and an increased risk of nonvertebral fractures in healthy euthyroid postmenopausal women. *Journal of Clinical Endocrinology and Metabolism*, **95**, 3173–3181.

19 Sugitani, I. & Fujimoto, Y. (2011) Effect of postoperative thyrotropin suppressive therapy on bone mineral density in patients with papillary thyroid carcinoma: a prospective controlled study. *Surgery*, **150**, 1250–1257.

20 Biondi, B., Filetti, S. & Schlumberger, M. (2005) Thyroid-hormone therapy and thyroid cancer: a reassessment. *Nature Clinical Practice Endocrinology & Metabolism*, **1**, 32–40.

21 Tuttle, R.M., Tala, H., Shah, J. *et al.* (2010) Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. *Thyroid*, **20**, 1341–1349.

22 Pacini, F, Castagna, MG, Brilli, L *et al.* (2012) Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* **23**(Suppl. 7), vii110–vii119.

23 Biondi, B. & Cooper, D.S. (2010) Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. *Thyroid*, **20**, 135–146.

24 Hovens, G.C., Stokkel, M.P., Kievit, J. *et al.* (2007) Associations of serum thyrotropin concentrations with recurrence and death in differentiated thyroid cancer. *Journal of Clinical Endocrinology and Metabolism*, **92**, 2610–2615.

25 Pujol, P., Daures, J.P., Nsakala, N. *et al.* (1996) Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. *Journal of Clinical Endocrinology and Metabolism*, **81**, 4318–4323.

26 Pacini, F, Castagna, MG, Brilli, L *et al.* (2012) Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* **23**(Suppl. 7), vii110–vii119.

27 Sugitani, I. & Fujimoto, Y. (2010) Does postoperative thyrotropin suppression therapy truly decrease recurrence in papillary

thyroid carcinoma? A randomized controlled trial. *Journal of Clinical Endocrinology and Metabolism*, **95**, 4576–4583.
28 Bauer, D.C., Ettinger, B., Nevitt, M.C., *et al.* (2001) Risk for fracture in women with low serum levels of thyroid-stimulating hormone. *Annals of Internal Medicine*, **134**, 561–568.
29 Leese, G.P., Jung, R.T., Guthrie, C., *et al.* (1992) Morbidity in patients on L-thyroxine: a comparison of those with a normal TSH to those with a suppressed TSH. *Clinical Endocrinology (Oxford)*, **37**, 500–503.
30 Flynn, R.W., Bonellie, S.R., Jung, R.T., *et al.* (2010) Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. *Journal of Clinical Endocrinology Metabolism*, **95**, 186–193.
31 WHO Fracture Risk Assessment Tool, 2008.
32 Kanis, J.A., Johnell, O., Oden, A. *et al.* (2008) FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporosis International*, **19**, 385–397.
33 Haymart, M.R., Cayo, M. & Chen, H. (2009) Papillary thyroid microcarcinomas: big decisions for a small tumor. *Annals of Surgical Oncology*, **16**, 3132–3139.
34 Balentine, C.J., Domingo, R.P., Patel, R. *et al.* (2013) Thyroid lobectomy for indeterminate FNA: not without consequences. *Journal of Surgical Research*, **184**, 189–192.
35 Johner, A., Griffith, O.L., Walker, B. *et al.* (2011) Detection and management of hypothyroidism following thyroid lobectomy: evaluation of a clinical algorithm. *Annals of Surgical Oncology*, **18**, 2548–2554.
36 Association of Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation. (2006) UK Guidelines for the Use of Thyroid Function Tests. ACB, London. Available from: http://www.british-thyroid-association.org/info-for-patients/Docs/TFT_guideline_final_version_July_2006.pdf (accessed 12 June 2014).
37 Vaisman, F., Momesso, D., Bulzico, D.A. *et al.* (2013) Thyroid lobectomy is associated with excellent clinical outcomes in properly selected differentiated thyroid cancer patients with primary tumors greater than 1 cm. *Journal of Thyroid Research*, **2013**, 398194. Doi: 10.1155/2013/398194. Epub 2013 Dec 23.
38 Durante, C., Montesano, T., Torlontano, M. *et al.* (2013) Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. *Journal of Clinical Endocrinology and Metabolism*, **98**, 636–42.
39 Demers, LM & Spencer, CA (2003) Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease. National Academy of Clinical Biochemistry, Washington, DC. http://www.aacc.org/sitecollectiondocuments/nacb/lmpg/thyroid/thyroidfullversionwithcover.pdf (accessed 12 June 2014).
40 Spencer, C.A., Bergoglio, L.M., Kazarosyan, M. *et al.* (2005) Clinical impact of thyroglobulin (Tg) and Tg autoantibody method differences on the management of patients with differentiated thyroid carcinomas. *Journal of Clinical Endocrinology and Metabolism*, **90**, 5566–5575.
41 Spencer, C. (2011) Clinical utility of thyroglobulin antibody (TgAb) measurements for patients with differentiated thyroid cancers (DTC). *Journal of Clinical Endocrinology and Metabolism*, **96**, 3615–3627.
42 Giovanella, L., Keller, F., Ceriani, L. *et al.* (2009) Heterophilic antibody interference in Tg assays can result in false positive and false negative results. *Clinical Chemistry and Laboratory Medicine*, **47**, 952–954.
43 Association of Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation. (2006) UK Guidelines for the Use of Thyroid Function Tests. ACB, London.
44 Feldt-Rasmussen, U., Petersen, P.H., Date, J. *et al.* (1982) Serum thyroglobulin in patients undergoing subtotal thyroidectomy for toxic and nontoxic goiter. *Journal of Endocrinological Investigation*, **5**, 161–164.
45 Izumi, M., Kubo, I., Taura, M. *et al.* (1986) Kinetic study of immunoreactive human thyroglobulin. *Journal of Clinical Endocrinology and Metabolism*, **62**, 410–412.
46 Hocevar, M., Auersperg, M. & Stanovnik, L. (1997) The dynamics of serum thyroglobulin elimination from the body after thyroid surgery. *European Journal of Surgical Oncology*, **23**, 208–210.
47 Ozata, M., Suzuki, S., Miyamoto, T. *et al.* (1994) Serum thyroglobulin in the follow-up of patients with treated differentiated thyroid cancer. *Journal of Clinical Endocrinology and Metabolism*, **79**, 98–105.
48 Kloos, R.T. & Mazzaferri, E.L. (2005) A single recombinant human thyrotrophin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. *Journal of Clinical Endocrinology and Metabolism*, **90**, 5047–5057.
49 Castagna, M.G., Brilli, L., Pilli, T. *et al.* (2008) Limited value of repeat recombinant thyrotropin (rhTSH)-stimulated thyroglobulin testing in differentiated thyroid carcinoma patients with previous negative rhTSHstimulated thyroglobulin and undetectable basal serum thyroglobulin levels. *Journal of Clinical Endocrinology and Metabolism*, **93**, 76–81.
50 Mazzaferri, E.L., Robbins, R.J., Braverman, L.E. *et al.* (2003) Pinchera An Authors' response: a consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism*, **88**, 4508–4509.
51 David, A, Blotta, A, Bondanelli, M *et al.* (2001) Serum thyroglobulin concentrations and (131)I whole-body scan results in patients with differentiated thyroid carcinoma after administration of recombinant human thyroid-stimulating hormone. *Journal of Nuclear Medicine* **42**, 1470–1475.
52 Mazzaferri, E.L. & Kloos, R.T. (2002) Is diagnostic iodine-131 scanning with recombinant human TSH (rhTSH) useful in the follow-up of differentiated thyroid cancer after thyroid ablation? *Journal of Clinical Endocrinology and Metabolism*, **87**, 1490–1498.
53 Haugen, B.R., Ridgway, E.C., McLaughlin, B.A. *et al.* (2002) Clinical comparison of whole-body radioiodine scan and serum thyroglobulin after stimulation with recombinant human thyrotropin. *Thyroid*, **12**, 37–43.
54 Lima, N., Cavaliere, H., Tomimori, E. *et al.* (2002) Prognostic value of serial serum thyroglobulin determinations after total thyroidectomy for differentiated thyroid cancer. *Journal of Endocrinological Investigation*, **25**, 110–115.
55 Wartofsky, L. (2002) Management of low-risk well-differentiated thyroid cancer based only on thyroglobulin measurement after recombinant human thyrotropin. *Thyroid*, **12**, 583–590.
56 Baudin, E, Do Cao, C, Cailleux, AF *et al.* (2003) Positive predictive value of serum thyroglobulin levels, measured during the first year of follow-up after thyroid hormone withdrawal, in thyroid cancer patients. *Journal of Clinical Endocrinology and Metabolism* **88**, 1107–1111.
57 Smallridge, R.C., Meek, S.E., Morgan, M.A. *et al.* (2007) Monitoring thyroglobulin in a sensitive iummunoassay has comparable sensitivity to recombinant human TSH-stimulated

thyroglobulin in follow-up of thyroid cancer patients. *The Journal of Clinical Endocrinology and Metabolism*, **92**, 82–7.

58 Iervasi, A., Iervasi, G., Ferdeghini, M. *et al.* (2007) Clinical Relevance of highly sensitive Tg assayin monitoring patients treated for differentiated thyroid cancer. *Clinical Endocrinology (Oxford)*, **67**, 434–41.

59 Malandrino, P., Latina, A., Marescalco, S. *et al.* (2011) Risk adapted management of differentiated thyroid cancer assessed by a sensitive measurement of basal serum thyroglobulin. *The Journal of Clinical Endocrinology and Metabolism*, **96**, 1703–1709.

60 Chindris, AM, Diehl, NN, Crook, JE *et al.* (2012) Undetectable sensitive serum thyroglobulin (<0.1 ng/ml) in 163 patients with follicular cell-derived thyroid cancer: results of rhTSH stimaulation and neck ultrasonography and long-term biochemical and clinical follow-up. *The Journal of Clinical Endocrinology and Metabolism* **97**, 2714–2723.

61 Spencer, C., Fatemi, S., Singer, P. *et al.* (2010) Serum Basal thyroglobulin measured by a second-generation asay correlates with the recombinant human thyrotropin-stimulated thyroglobulin response in patients treated for differentiated thyroid cancer. *Thyroid*, **20**, 587–595.

62 Castaga, MG, Tala Jury, HP, Cipri, C *et al.* (2011) The use of ultrasensitive thyroglobulin assays reduces but does not abolish the need for TSH stimulation in patients with differentiated thyroid carcinoma. *Journal of Endocrinological Investigation* **34**, 219–223.

63 Pacini, F., Schlumberger, M., Dralle, H. *et al.* (2006) European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *European Journal of Endocrinology*, **154**, 787–803.

64 Schlumberger, M., Berg, G., Cohen, O. *et al.* (2004) Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. *European Journal of Endocrinology*, **150**, 105–112.

65 Mazzaferri, E.L., Robbins, R.J., Spencer, C.A. *et al.* (2003) A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism*, **88**, 1433–1441.

66 Luster, M., Lippi, F., Jarzab, B. *et al.* (2005) rhTSH-aided radioiodine ablation and treatment of differentiated thyroid carcinoma: a comprehensive review. *Endocrine-Related Cancer*, **12**, 49–64.

67 Haugen, B.R., Pacini, F., Reiners, C. *et al.* (1999) A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *Journal of Clinical Endocrinology and Metabolism*, **84**, 3877–3885.

68 Haugen, BR, Pacini, F, Reiners, C *et al.* (1999) A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. *Journal of Clinical Endocrinology and Metabolism* **84**, 3877–3885.

69 Lee, J., Yun, M.J., Nam, K.H. *et al.* (2010) Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. *Thyroid*, **20**, 173–179.

70 Borget, I., Corone, C., Nocaudie, M. *et al.* (2007) Sick leave for follow-up control in thyroid cancer patients: comparison between stimulation with Thyrogen and thyroid hormone withdrawal. *European Journal of Endocrinology*, **156**, 531–538.

71 Mernagh, P., Suebwongpat, A., Silverberg, J. *et al.* (2010) Cost-effectiveness of using recombinant human thyroid-stimulating hormone before radioiodine ablation for thyroid cancer: the Canadian perspective. *Value Health*, **13**, 180–187.

72 Luster, M., Lippi, F., Jarzab, B. *et al.* (2005) rhTSH-aided radioiodine ablation and treatment of differentiated thyroid carcinoma: a comprehensive review. *Endocrine-Related Cancer*, **12**, 49–64.

CHAPTER 12

12 Recurrent/persistent differentiated thyroid cancer

Early detection of recurrent disease can lead to cure or certainly long-term survival, particularly if the disease is operable or takes up ^{131}I.[1–10] Distant metastases develop in 5–23% of patients with differentiated thyroid cancer (DTC), mainly in the lungs and bones.

i Detection of abnormal masses in the neck or elsewhere should lead to fine-needle aspiration cytology and other appropriate investigations (**4, D**).

12.1. Recurrence in the thyroid bed or cervical lymph nodes

Surgical re-exploration is the preferred method of management, usually followed by ^{131}I therapy[11,12] in patients with macroscopic residual disease. Recurrent neck disease uncontrolled by surgery and ^{131}I therapy may be treated by high-dose external beam radiotherapy (EBRT) (Chapter 10). As patients are likely to survive for a significant period, radical EBRT can be considered (Chapter 10.2) with daily fractionation and meticulous radiotherapy planning techniques.[13,14] Consideration of entry into clinical trials is also encouraged.

While the strategy outlined above is applicable in high risk cases (for definition of high risk see Chapter 2.3, Table 2.2), the efficacy of an aggressive approach in slow growing tumours is less well established. In these cases, if sensitive diagnostic techniques (high-definition ultrasonography (US), stimulated serum thyroglobulin (sTg) measurements) indicate very low volume disease in the neck, then observation is an option whilst monitoring symptoms and rate of progression.

i Surgery with curative intent is the treatment of choice for recurrent disease confined to the neck (**2+ C**).

Key recommendation

ii Low volume recurrent or persistent disease in the neck, which is not progressive, may be treated either by surgery or managed with active surveillance (**4 D**).

iii Residual macroscopic disease in the neck following surgery for recurrent disease may be treated with ^{131}I (**4, D**).

iv Patients with progressive disease in the neck not amenable to surgery and unresponsive to ^{131}I should be considered for EBRT (**4, D**).

v Patients with distant metastases who have recurrent disease in the neck (lymph node/thyroid bed) or mediastinum should be considered for reoperative surgery on a case by case basis if loss of loco-regional control would result in compromise of the aerodigestive tract or soft tissues in the neck. (**4, D**).

12.2. Metastatic disease involving lung and other soft tissue areas

If the tumour takes up ^{131}I long-term survival is possible in patients with lung and soft tissue metastases. For further details on ^{31}I therapy for metastatic disease, see Chapter 9.3.

i Metastases involving lungs and soft tissues are usually not amenable to surgery and should be treated with ^{131}I therapy[2,15–18] (**2−, D**).

Patients with metastatic disease will require support from the clinical team and access to good quality information (Appendix 4, Patient Information Leaflet 6).

Good Practice Point ☑

12.3. Bone metastases

Extensive bone metastases are generally not curable by ^{131}I therapy alone. For solitary or a limited number of bone metastases that are not cured by ^{131}I therapy, EBRT (Chapter 10.3) with/without resection and/or embolisation/thermal ablation or cement injection may be beneficial in selected cases. EBRT also has an important role in the management of spinal cord compression due to vertebral metastases in addition to surgery[13] (Chapter 10).

In the palliative setting, pamidronate has been shown in a small study to improve pain from bone metastases in patients with thyroid cancer.[19] Evidence from other cancers suggests that bisphosphonate therapy with zoledronic acid, is associated with reduced skeletal-related events (SRE) defined as pathological fracture, spinal cord compression, radiation therapy, or surgery to bone.[20] Besides bisphosphonates, denosumab therapy may also be beneficial.[21,22]

i Solitary or limited bone metastases unresponsive to ^{131}I should be considered for further treatment with one or more of the following modalities: EBRT, surgical resection, embolisation, thermal ablation, cement injection (**3, D**).

ii Bisphosphonates or denosumab should be considered in patients with bone metastases (**4, D**).

12.4. Cerebral metastases

Patients with oligometastases in the brain from DTC, may benefit from resection or radiosurgery. If the patient is fit and has a life expectancy of at least 3 months, EBRT has an important palliative role in the management of cerebral metastases (Chapter 10.3) along with surgery if appropriate.[13]

i Patients with oligometastases and good performance status should be considered for surgical resection or radiosurgery **(1++, B).**

ii Patients with known brain metastases should initially be considered for resection or EBRT followed by ^{131}I therapy (unless the metastases have been proven to be ^{131}I refractory) **(3, D).**

iii Patients with unresectable cerebral metastases should be treated with EBRT **(4, D).**

iv Cerebral radiotherapy should be used carefully in patients with poor performance status as the side effects may outweigh the benefits **(2−, D).**

12.5. Other metastatic sites

i In selected cases when there are a limited number of metastases, metastasectomy, radiofrequency ablation or embolisation should be considered **(3, D).**

ii ^{131}I therapy should be offered to patients with ^{131}I sensitive metastases **(4, D).**

12.6. Management of patients with an elevated serum thyroglobulin

Occasionally the serum thyroglobulin (Tg) may be falsely increased by Tg antibodies, which may not always be measurable (Appendix 1). A serial rise in serum Tg is of more significance than one high result. Sometimes serum Tg declines slowly over years after ^{131}I treatment. If increased, serum Tg should be repeated to confirm the result prior to initiating investigations or treatment. Tumour is rarely found when stimulated Tg is <2 μg/l.[23] This threshold however may not be applicable for many of the currently available assays because of known differences in sensitivity, accuracy and precision (Appendix 1) and ideally cut-off values with corresponding sensitivity and specificity for detecting recurrent/persistent disease need to be established for the specific assay and patient population.

^{131}I whole body scan (WBS) is used less frequently to investigate elevated serum Tg, due to its inferior sensitivity for detecting locoregional disease compared to neck ultrasound (US). A challenging scenario is the US-negative, Tg-positive patient. Scans to consider performing (when the neck US is negative) include;

- chest CT without contrast;
- ^{18}fluoro-deoxy-glucose (FDG)-positron emission tomography (PET)-CT;
- neck MRI;
- CT;
- spine MRI[24];
- bone scan;
- ^{131}I WBS;
- very occasionally ^{111}In octreotide[25] or ^{68}Ga DOTATATE PET-CT[26] may be positive.

FDG-PET-CT is useful in this setting,[27–30] particularly if the Tg is significantly increased. FDG is concentrated by metabolically active thyroid cells and uptake indicates histologic transformation from low to high risk poor prognosis tumours, as FDG uptake reflects dedifferentiation. Thyroid hormone withdrawal (THW)[31] or recombinant human TSH (rhTSH) administration[32] have been shown to increase the sensitivity of FDG-PET-CT scan. Patients with positive FDG-PET-CT scan have been shown to have a markedly reduced 3-year survival compared with FDG-PET-CT scan-negative patients.[33] If PET imaging is positive, ^{131}I imaging is typically negative and the patient is ^{131}I refractory. Exactly which imaging modalities should be used and in which sequence is uncertain.

i A single elevated serum Tg should be confirmed by repeating the test before proceeding to additional investigations **(4, D).**

ii An elevated serum Tg should lead to a detailed neck US **(2+, C).**

iii For patients with low concentrations of Tg that are not rising, the decision to proceed to further investigations needs to be balanced against the low probability of detecting the site of disease for which treatment would be beneficial to the patient **(4, D).**

iv The choice of imaging should be guided in the first instance by the symptoms and clinical assessment of the patient, which may point to a particular anatomical area, bearing in mind that the commonest sites of recurrent disease are cervical/mediastinal lymph nodes, lungs and bones **(4, D).**

Key recommendation

v As first line, any of the following imaging modalities may be used: chest CT without contrast, rhTSH-stimulated FDG-PET-CT, neck MRI, spine MRI, bone scan **(4, D).**

If diagnostic imaging fails to identify the source of raised Tg, empirical ^{131}I treatment may be given. Factors that should be considered in making this decision include the risk category (Chapter 2.3, Table 2.2) of the patient and the rate of rise of the serum Tg.[34]

There is no evidence from randomised controlled trials (RCTs) for or against empirical ^{131}I. Non-RCTs have reported abnormal uptake on the post-treatment WBS in 61% of patients[30] thereby localising and possibly treating a previously undiagnosed recurrence. The activity of empirical ^{131}I therapy used is usually 3·7–5·5 GBq.[35–37]

i It is uncertain whether empirical ^{131}I treatment is beneficial in patients with raised serum Tg, compared to active surveillance. A **Personalised Decision Making** approach is recommended in such cases (Chapter 2, 4) **(4, D).**

ii The combination of a positive diagnostic ^{131}I scan and an undetectable serum Tg is very rare in the absence of Tg antibody interference. In such cases the possibility of false positivity should be adequately explored before administering further ^{131}I therapy[38] **(2+, C).**

iii 3·7–5·5 GBq is a commonly used activity for persistent or recurrent disease **(4 D).**

iv If the post-treatment WBS is negative, no further ^{131}I is advised unless there is a significant decrease in serum Tg concentration **(4, D).**

Data for the use of therapy with radiolabelled somatostatin analogues in patients with oncocytic follicular (Hürthle cell) carcinoma and dedifferentiated papillary carcinoma are limited,[39]

but could be considered if there is significant tumour uptake on a somatostatin scan **(4, D).**

12.7. Palliative care

Palliative care is not necessary in the vast majority of patients with DTC because they are usually cured. However, in the small proportion of patients with recurrent or end-stage disease specialist palliative care input is advised.

i The MDT should work closely with nominated palliative medicine colleagues and patients requiring palliative care input should be referred early to their local team[40] **(4, D).**

Palliative EBRT. Palliative EBRT to localised areas of symptomatic metastatic disease may be appropriate in good performance status patients with anticipated survival of more than 6 months. EBRT also has a role in palliation of symptoms from bone metastases, fungating lymph nodes, bleeding tumour, stridor, and dysphagia (Chapter 10).

Stridor and fear of choking are very distressing and can also be alleviated by pharmacological means, palliative surgery (e.g. laser/radiofrequency ablation, stents) and counselling.

Palliative chemotherapy. Palliative chemotherapy has largely been superseded by targeted therapies (see next section). It can however be considered in good performance status patients with rapidly progressive, symptomatic, ^{131}I refractory, locally advanced or metastatic disease when targeted therapies are unavailable or have proved unsuccessful. The agents used are doxorubicin and cisplatin, but durable responses are uncommon.[41,42] **(4, D).**

Targeted therapies for DTC. Efficacy for progression-free survival, but not overall survival, has been demonstrated for several agents in phase 2 or 3 studies including axitinib, motesanib, sorafenib, pazopanib, lenvatinib, sunitinib, cabozantinib, vandetanib and thalidomide. The agents demonstrating the most activity and clinical benefit to date are sorafenib and lenvatinib. A randomised phase 3 trial of sorafenib versus placebo resulted in a progression free survival benefit of 5 months for patients on sorafenib over those on placebo (10·8 *vs* 5·8 months; hazard ratio 0·587, 95% CI 0·454, 0·758, $P < 0·0001$).[43] Early data have shown good response rates in BRAF V600E mutated papillary carcinoma with vemurafanib a potent inhibitor of the oncogenic BRAF protein kinase.[44,45] Studies continue to evaluate the role of molecular profiling in determination of the most appropriate targeted agent. The use of targeted therapies is a rapidly evolving area and clear guidance cannot be given at present.

i The use of targeted therapies outside clinical trials should be endorsed by the MDM after careful consideration of the balance between potential benefits and harm **(4, D).**
ii The principal indication for targeted treatments is radiologically progressive, symptomatic disease, refractory to conventional treatments **(4, D).**
iii Targeted therapies should only be administered in the setting of cancer units that have experience in monitoring and managing adverse effects of targeted therapies **(4, D).**
iv Consideration should therefore be given to entry into clinical studies **(4, D).**

Information on current trial activity can be found at:

http://public.ukcrn.org.uk/search/Portfolio.aspx?Level1=1&Level2=7;
www.clinicaltrials.gov;
www.nci.nih.gov;
www.centerwatch.com;
www.thyroid.org.

References

1 Mazzaferri, E.L. (1999) An overview of the management of papillary and follicular thyroid carcinoma. *Thyroid*, **9**, 421–427.
2 Mazzaferri, E.L. & Jhiang, S.M. (1994) Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *American Journal of Medicine*, **97**, 418–428.
3 Cooper, D.S., Doherty, G.M., Haugen, B.R. *et al.* (2006) Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*, **16**, 109–142.
4 Pacini, F., Schlumberger, M., Dralle, H. *et al.* (2006) European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *European Journal of Endocrinology*, **154**, 787–803.
5 Mazzaferri, E.L. (2006) An overview of the management of thyroid cancer. In: E.L. Mazzaferri, C. Harmer, U.K. Mallick, P. Kendall-Taylor eds. Practical Management of Thyroid Cancer: A Multidisciplinary Approach. Springer, London, 1–28.
6 Thyroid Carcinoma Task Force (2001) AACE/AAES Medical/Surgical Guidelines for Clinical Practice: Management of Thyroid Carcinoma. American Association of Clinical Endocrinologists, Jacksonville, FL. Available from: https://www.aace.com/files/thyroid-carcinoma.pdf (accessed 12 June 2014).
7 Reiners, C. & Farahati, J. (1999) I^{131} therapy of thyroid cancer patients. *Quarterly Journal of Nuclear Medicine*, **43**, 324–335.
8 Harmer, C.L. & McCready, V.R. (1996) Thyroid cancer: differentiated carcinoma. *Cancer Treatment Reviews*, **22**, 161–177.
9 Taylor, T., Specker, B., Robbins, J. *et al.* (1998) Outcome after treatment of high risk papillary and non-Hurthle-cell follicular thyroid carcinoma. *Annals of Internal Medicine*, **129**, 622–627.
10 Kebebew, E. & Clark, O.H. (2000) Differentiated thyroid cancer 'complete' rational approach. *World Journal of Surgery*, **24**, 942–951.
11 Schlumberger, M.J. (1998) Papillary and follicular thyroid carcinoma. *New England Journal of Medicine*, **338**, 297–306.
12 Tsang, R.W., Brierley, J.D., Simpson, W.J. *et al.* (1998) The effects of surgery, radioiodine and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. *Cancer*, **82**, 375–388.
13 Haq, M. & Harmer, C. (2006) Non-surgical management of thyroid cancer. In: E.L. Mazzaferri, C. Harmer, U.K. Mallick, P. Kendall-Taylor eds. Practical Management of Thyroid Cancer: A Multidisciplinary Approach. Springer, London, 171–191.
14 Meadows, K.M., Amdur, R.J., Morris, C.G. *et al.* (2006) External beam radiotherapy for differentiated thyroid cancer. *American Journal of Otolaryngology*, **27**, 24–28.
15 Maxon, H.R. & Smith, H.S. (1990) Radioiodine-131 in the diagnosis and treatment of metastatic well differentiated thyroid cancer.

Endocrinology and Metabolism Clinics of North America, **19**, 685–718.
16 Brown, A.P., Greening, W.P., McCready, V.R. *et al.* (1984) Radioiodine treatment of metastatic thyroid carcinoma: the Royal Marsden Hospital experience. *British Journal of Radiology*, **57**, 323–327.
17 Wilson, P.C., Millar, B.M. & Brierley, J.D. (2004) The management of advanced thyroid cancer. *Clinical Oncology (Royal College of Radiologist)*, **16**, 561–568.
18 Van Nostrand, D., Atkins, F., Yeganeh, F. *et al.* (2002) Dosimetrically determined doses of radioiodine for the treatment of metastatic thyroid carcinoma. *Thyroid*, **12**, 121–134.
19 Vitale, G., Fonderico, F., Martignetti, A. *et al.* (2001) Pamidronate improves the quality of life and induces clinical remission of bone metastases in patients with thyroid cancer. *British Journal of Cancer*, **84**, 1586–1590.
20 Polascik, T.J. (2009) Bisphosphonates in oncology: evidence for the prevention of skeletal events in patients with bone metastases. *Drug Design, Development and Therapy*, **3**, 27–40.
21 Wexler, J.A. (2011) Approach to the thyroid cancer patient with bone metastases. *Journal of Clinical Endocrinology and Metabolism*, **96**, 2296–2307.
22 Henry, D.H., Costa, L., Goldwasser, F. *et al.* (2011) Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *Journal of Clinical Oncology*, **29**, 1125–1132.
23 Mazzaferri, E.L., Robbins, R.J., Spencer, C.A. *et al.* (2003) A consensus report of the role of serum thyroglobulin as a monitoring method for low risk patients with papillary thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism*, **88**, 1433–1441.
24 Schmidt, G.P., Schoenberg, S.O., Schmid, R. *et al.* (2007) Screening for bone metastases: whole-body MRI using a 32-channel system versus dual-modality PET-CT. *European Radiology*, **17**, 939–949.
25 Christian, J.A., Cook, G.J. & Harmer, C. (2003) Indium-111-labelled octreotide scintigraphy in the diagnosis and management of non-iodine avid metastatic carcinoma of the thyroid. *British Journal of Cancer*, **89**, 258–261.
26 Ocak, M., Demirci, E., Kabasakal, L. *et al.* (2013) Evaluation and comparison of Ga-68 DOTA-TATE and Ga-68 DOTA-NOC PET/CT imaging in well-differentiated thyroid cancer. *Nuclear Medicine Communications*, **34**, 1084–1089.
27 Saghari, M., Gholamrezanezhad, A., Mirpour, S. *et al.* (2006) Efficacy of radioiodine therapy in the treatment of elevated serum thyroglobulin in patients with differentiated thyroid carcinoma and negative whole-body iodine scan. *Nuclear Medicine Communications*, **27**, 567–572.
28 Alzahrani, A.S., Mohamed, G., Al Shammary, A. *et al.* (2005) Long-term course and predictive factors of elevated serum thyroglobulin and negative diagnostic radioiodine whole body scan in differentiated thyroid cancer. *Journal of Endocrinological Investigation*, **28**, 540–546.
29 Gutiérrez Cardo, A.L., Rodríguez Rodríguez, J.R., Borrego Dorado, I. *et al.* (2007) Patients treated for differentiated thyroid cancer with negative ^{131}I whole-body scans and elevated thyroglobulin levels: a possible course. *Revista Española de Medicina Nuclear*, **26**, 138–145.
30 Chao, M. (2010) Management of differentiated thyroid cancer with rising thyroglobulin and negative diagnostic radioiodine whole body scan. *Clinical Oncology (Royal College of Radiologists (Great Britain))*, **22**, 438–447.
31 van Tol, K.M., Jager, P.L., Piers, D.A. *et al.* (2002) Better yield of (18)fluorodeoxyglucose- positron emission tomography in patients with metastatic differentiated thyroid carcinoma during thyrotropin stimulation. *Thyroid*, **12**, 381–387.
32 Petrich, T., Borner, A.R., Otto, D. *et al.* (2002) Influence of rhTSH on 18-fluorodeoxyglucose uptake by differentiated thyroid carcinoma. *European Journal of Nuclear Medicine and Molecular Imaging*, **29**, 641–647.
33 Wang, W., Larson, S.M., Fazzari, M. *et al.* (2000) Prognostic value of [18F]fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. *The Journal of Clinical Endocrinology and Metabolism*, **85**, 1107–1113.
34 Mazzaferri, E.L. (2006) Management of differentiated thyroid carcinoma in patients with negative whole-body radioiodine scans and elevated serum thyroglobulin levels. In: E.L. Mazzaferri, C. Harmer, U.K. Mallick, P. Kendall-Taylor eds. Practical Management of Thyroid Cancer: A Multidisciplinary Approach. Springer, London, 237–254.
35 Schlumberger, M., Mancusi, F., Baudin, E. *et al.* (1997) 131-I therapy for elevated thyroglobulin levels. *Thyroid*, **7**, 273–276.
36 van Tol, K.M., Jager, P.L., de Vries, E.G. *et al.* (2003) Outcome in patients with differentiated thyroid cancer with negative diagnostic whole-body scanning and detectable stimulated thyroglobulin. *European Journal of Endocrinology*, **148**, 589–596.
37 Pineda, J.D., Lee, T., Ain, K. *et al.* (1995) Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. *Journal of Clinical Endocrinology and Metabolism*, **80**, 1488–1492.
38 Carlisle, M.R., Lu, C. & McDougall, I.R. (2003) The interpretation of 131I scans in the evaluation of thyroid cancer, with an emphasis on false positive findings. *Nuclear Medicine Communications*, **24**, 715–735.
39 Teunissen, J.J., Kwekkeboom, D.J., Kooij, P.P. *et al.* (2005) Peptide receptor radionuclide therapy for non radioiodine avid differentiated thyroid cancer. *Journal of Nuclear Medicine*, **46**, 107–114.
40 Comisky, M. (2006) Specialist palliative care for anaplastic thyroid carcinoma. In: E.L. Mazzaferri, C. Harmer, U.K. Mallick, P. Kendall-Taylor eds. Practical Management of Thyroid Cancer: A Multidisciplinary Approach. Springer, London, 411–419.
41 Shimaoka, K., Schoenfeld, D.A., Dewys, W.D. *et al.* (1985) A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid cancer. *Cancer*, **56**, 2155–2160.
42 Williams, S.D., Birch, R. & Einhorn, L.H. (1986) Phase II evaluation of doxorubicin plus cisplatin in advanced thyroid cancer: a Southeastern Cancer Study Group Trial. *Cancer Treatment Reports*, **70**, 405–407.
43 Brose, M., Nutting, C., Jarzab, B. *et al.* (2013) Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: the phase III DECISION trial. *Journal of Clinical Oncology* **31**(suppl), abstr 4.
44 Dadu, R., Devine, C., Hernandez, M., *et al.* (2014) Role of salvage targeted therapy in differentiated thyroid cancer patients who failed first-line sorafenib. *Journal of Clinical Endocrinology and Metabolism*, **99**, 2086–2094.
45 Kim, K.B., Cabanillas, M.E., Lazar, A.J. *et al.* (2013) Clinical responses to vemurafenib in patients with metastatic papillary thyroid cancer harboring BRAF(V600E) mutation. *Thyroid*, **23**, 1277–1278.

CHAPTER 13

13 Long-term follow-up of differentiated thyroid cancer

The long-term follow-up schedule of patients with a previous diagnosis of differentiated thyroid cancer (DTC) depends on risk.

i Patients who have undergone hemithyroidectomy alone because of the low risk of recurrence (Chapters 7 and 8) do not require TSH suppression or long-term follow-up in secondary care (Chapter 8.3). For all other patients, regular follow-up of DTC 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 protocols **(4, D).**

ii Once the thyroid remnant has been ablated and following Dynamic Risk Stratification (Chapter 2.3, Table 2.3), the frequency of attendance will be decided in each case individually:

- Patients with excellent response (Table 2.3) do not require TSH suppression (Chapter 11.5) and should be followed 6 monthly for the first year, and annually thereafter **(4, D).**
- Patients with indeterminate or incomplete response should be followed up more frequently depending on individual need **(4, D).**

iii Support and counselling may be necessary, particularly for younger patients, and in relation to pregnancy.

iv Follow-up for patients who have received radioiodine remnant ablation (RRA) or ^{131}I therapy should be lifelong **(4, D)** for the following reasons:

- 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 ^{131}I treatment may develop, such as leukaemia or second tumours.

v Low-risk cases (for definition of low risk, see Chapter 2.3, Table 2.2) who have completed their treatment, are 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 multidisciplinary thyroid cancer clinic. This may include a nurse-led clinic or primary care following agreement of well defined protocols and re-referral pathways **(4, D).**

Key recommendation

vi At each visit the following tasks should be completed **(4, D):**

- Patient history should be taken.
- A clinical examination should be performed.
- Adequacy of TSH suppression and possible effects of thyrotoxicosis should be assessed.
- Tg should be measured as a marker of tumour recurrence. TgAb should be measured simultaneously with measurement of Tg (Appendix 1).
- The calcium status should be assessed in patients receiving treatment for hypoparathyroidism (Chapter 11.3).

CHAPTER 14

14 Thyroid nodules and thyroid cancer in pregnancy

14.1. Thyroid nodules in pregnancy

The prevalence of thyroid nodules in pregnancy is reported to range between 3% and 21% and increases with maternal age and parity.[1–4] The optimal diagnostic strategy for thyroid nodules detected during pregnancy is based on risk stratification.

Pregnancy does not affect the accuracy or interpretation of cytological specimens, although the reliability of fine-needle aspiration cytology (FNAC) has not been investigated in prospective studies. Thyroid or lymph node FNAC confers no additional risk to the pregnancy at any stage of gestation.[5,6]

i All women presenting with a thyroid nodule during pregnancy should undergo the following: a complete history and clinical examination, serum thyroid stimulating hormone (TSH) testing and neck ultrasound (US),[6,7] in line with the recommendations in Chapter 4 (**2+, C**).

ii Radioiodine scans are contraindicated in pregnancy and during breastfeeding **(4, C).**

iii In instances in which nodules on US are indeterminate/equivocal (U3, Chapter 4), FNAC may be deferred until after delivery based on the patients' preference[5,6] (**2+, C**).

iv Pregnant patients with an FNAC result that is indeterminate (Thy3a or Thy3f) or suspicious of papillary thyroid cancer (Thy4), do not require surgery while pregnant except in cases of rapid nodular growth and/or the appearance of lymph node metastases[6] (**4, D**).

14.2. Diagnosis of thyroid cancer in pregnancy

The management of thyroid cancer diagnosed during pregnancy requires careful consideration of risks to both the mother and foetus. Thyroid cancer discovered during pregnancy does not behave more aggressively than that diagnosed in a similar aged group of non-pregnant women. Pregnant women with thyroid cancer generally have an excellent prognosis, similar to that of non-pregnant women of childbearing age.[8,9]

Surgery is the treatment of choice and may be indicated in case of rapid tumour growth or in the presence of significant lymph node metastases.[5,6] Thyroidectomy may be performed safely in the second trimester when overall maternal and foetal complication rates are low. Lower complication rates were observed in high volume centres with experienced surgeons.[10] Surgery performed during the first and third trimester of pregnancy is associated with increased risks of abortion, altered organogenesis, and preterm labour and delivery respectively.[6,11] Deferring surgery until the postpartum has not been associated with a worse prognosis.

i Discussion of the case by the multidisciplinary team (MDT), as well as counselling of the couple, are imperative **(4, D).**

ii ^{131}I ablation or therapy must be avoided in pregnancy **(4, D).**

iii If thyroid cancer is diagnosed or suspected, the following options should be considered **(4, D):**

- Defer thyroidectomy, and other treatments until the postpartum period.
- Perform a thyroidectomy during the second trimester of pregnancy, to be followed by suppressive doses of levothyroxine to achieve suppressed but detectable serum TSH concentrations and high normal serum free thyroxine (fT4) concentrations.

iv There is no evidence to recommend for or against suppression of serum TSH concentrations in pregnant women who elect to defer surgery for differentiated thyroid cancer (DTC) until after delivery[5,6] (**4, D**).

v When a decision has been made to defer surgery until after delivery, patients may require on-going reassurance, especially if the diagnosis is made at the beginning of pregnancy. It is **Good Clinical Practice** ☑ for the patient to:

- receive good quality information on options/risks
- receive expert guidance on decision making
- be offered an appointment every few months during pregnancy in order to have the opportunity to discuss her management
- have the option not to attend if she does not feel there is a need to
- be able to talk to or be seen by the expert at other times if concerned
- have the reassurance that other professionals involved (midwife, GP, obstetrician) are kept fully informed
- make contact with the expert nearer the time of delivery, in order to plan the timing of surgery.

iv The diagnosis or suspicion of medullary thyroid cancer or other rare types with more aggressive potential than DTC requires consideration of treatment during pregnancy **(4, D).**

14.3. Pregnancy in the treated patient with thyroid cancer

Exposure of the foetus to radiation is potentially harmful.[10,12] A small risk of spontaneous abortion may persist for up to 1 year after high-dose ^{131}I remnant ablation (RRA) or therapy and this may relate to suboptimal thyroid hormonal control.[8,13–16] The possible deleterious effects of radiation on gonadal function and the outcome of subsequent pregnancies have been reviewed.[17,18] There is no evidence that previous exposure to ^{131}I affects the

outcomes of subsequent pregnancies and offspring, provided the recommendations are followed.[6]

i In accordance with Administration of Radioactive Substances Advisory Committee (ARSAC), it is recommended that women should defer attempting conception for a minimum of 6 months and men for a period of 4 months following ^{131}I ablation or therapy[12] **(4, D).**

ii The pre-conception TSH goal in women with DTC, which is determined by risk stratification (Chapter 11.5), should be maintained during pregnancy.[5,6] The dose of levothyroxine needs to be empirically increased as soon as pregnancy is confirmed, usually by approximately 30%, as requirements increase during pregnancy[19–22] except in women receiving suppressive doses of levothyroxine **(2++, B).**

Key recommendation

iii Thyroid function should be evaluated as soon as pregnancy is confirmed. The adequacy of levothyroxine treatment should be monitored approximately every 4 weeks until 16–20 weeks of gestation and at least once per trimester thereafter. Serum TSH should be checked 4 weeks after each levothyroxine dose change[5,6,22,23] **(3, D).**

Key recommendation

iv US and thyroglobulin (Tg) monitoring should be performed each trimester during pregnancy in patients with previously treated thyroid cancer who are known, or suspected of having, recurrent disease. This is not required in low risk patients in whom evidence of persistent disease is absent[5,6,24–26] **(3, D)**.

v The management of pregnant women with persistent or recurrent thyroid cancer should be discussed by the MDT and treatment should be undertaken in a specialist centre[11] **(4, D)**.

vi Breastfeeding must be discontinued at least 8 weeks before radioiodine remnant ablation (RRA) or ^{131}I therapy to avoid breast irradiation and should not be resumed, until after a future pregnancy (Chapter 9.2) **(4, D).**

Key recommendation

References

1 Glinoer, D., Soto, M.F., Bourdoux, P. *et al.* (1991) Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. *Journal of Clinical Endocrinology and Metabolism*, **73**, 421–427.

2 Karger, S., Schotz, S., Stumvoll, M. *et al.* (2010) Impact of pregnancy on prevalence of goitre and nodular thyroid disease in women living in a region of borderline sufficient iodine supply. *Hormone and Metabolic Research*, **42**, 137–142.

3 Kung, A.W., Chau, M.T., Lao, T.T. *et al.* (2002) The effect of pregnancy on thyroid nodule formation. *Journal of Clinical Endocrinology and Metabolism*, **87**, 1010–1014.

4 Struve, C.W., Haupt, S. & Ohlen, S. (1993) Influence of frequency of previous pregnancies on the prevalence of thyroid nodules in women without clinical evidence of thyroid disease. *Thyroid*, **3**, 7–9.

5 De, G.L., Abalovich, M., Alexander, E.K. *et al.* (2012) Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*, **97**, 2543–2565.

6 Stagnaro-Green, A., Abalovich, M., Alexander, E. *et al.* (2011) Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid*, **21**, 1081–1125.

7 Papini, E., Guglielmi, R., Bianchini, A. *et al.* (2002) Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. *Journal of Clinical Endocrinology and Metabolism*, **87**, 1941–1946.

8 Moosa, M. & Mazzaferri, E.L. (1997) Outcome of differentiated thyroid cancer diagnosed in pregnant women. *Journal of Clinical Endocrinology and Metabolism*, **82**, 2862–2866.

9 Yasmeen, S., Cress, R., Romano, P.S. *et al.* (2005) Thyroid cancer in pregnancy. *International Journal of Gynaecology and Obstetrics*, **91**, 15–20.

10 Fushiki, S. (2013) Radiation hazards in children – lessons from Chernobyl, Three Mile Island and Fukushima. *Brain and Development*, **35**, 220–227.

11 Kuy, S., Roman, S.A., Desai, R. *et al.* (2009) Outcomes following thyroid and parathyroid surgery in pregnant women. *Archives of Surgery*, **144**, 399–406.

12 Administration of Radioactive Substances Advisory Committee (2006) Notes for Guidance on Clinical Administration of Radiopharmaceuticals and Use of Sealed Radioactive Sources. HPA, London. Available from: http://www.arsac.org.uk/notes_for_guidance/documents/ARSACNFG2006Corrected06-11-07.pdf (accessed 12 June 2014).

13 Ayala, C., Navarro, E., Rodriguez, J.R. *et al.* (1998) Conception after iodine-131 therapy for differentiated thyroid cancer. *Thyroid*, **8**, 1009–1011.

14 Casara, D., Rubello, D., Saladini, G. *et al.* (1993) Pregnancy after high therapeutic doses of iodine-131 in differentiated thyroid cancer: potential risks and recommendations. *European Journal of Nuclear Medicine*, **20**, 192–194.

15 Dottorini, M.E., Lomuscio, G., Mazzucchelli, L. *et al.* (1995) Assessment of female fertility and carcinogenesis after iodine-131 therapy for differentiated thyroid carcinoma. *Journal of Nuclear Medicine*, **36**, 21–27.

16 Schlumberger, M., de, V.F., Ceccarelli, C. *et al.* (1996) Exposure to radioactive iodine-131 for scintigraphy or therapy does not preclude pregnancy in thyroid cancer patients. *Journal of Nuclear Medicine*, **37**, 606–612.

17 Garsi, J.P., Schlumberger, M., Rubino, C. *et al.* (2008) Therapeutic administration of 131I for differentiated thyroid cancer: radiation dose to ovaries and outcome of pregnancies. *Journal of Nuclear Medicine*, **49**, 845–852.

18 Sawka, A.M., Lakra, D.C., Lea, J. *et al.* (2008) A systematic review examining the effects of therapeutic radioactive iodine on ovarian function and future pregnancy in female thyroid cancer survivors. *Clinical Endocrinology*, **69**, 479–490.

19 Loh, J.A., Wartofsky, L., Jonklaas, J. *et al.* (2009) The magnitude of increased levothyroxine requirements in hypothyroid pregnant women depends upon the etiology of the hypothyroidism. *Thyroid*, **19**, 269–275.

20 Alexander, E.K., Marqusee, E., Lawrence, J. *et al.* (2004) Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *New England Journal of Medicine*, **351**, 241–249.

21 Mandel, S.J., Larsen, P.R., Seely, E.W. *et al.* (1990) Increased need for thyroxine during pregnancy in women with primary hypothyroidism. *New England Journal of Medicine*, **323**, 91–96.

22 Yassa, L., Marqusee, E., Fawcett, R. *et al.* (2010) Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. *Journal of Clinical Endocrinology and Metabolism*, **95**, 3234–3241.
23 Association of Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation (2006) UK Guidelines for the Use of Thyroid Function Tests. ACB, London. www.acb.org.uk/docs/TFTguidelinefinal.
24 Hirsch, D., Levy, S., Tsvetov, G. *et al.* (2010) Impact of pregnancy on outcome and prognosis of survivors of papillary thyroid cancer. *Thyroid*, **20**, 1179–1185.
25 Leboeuf, R., Emerick, L.E., Martorella, A.J. *et al.* (2007) Impact of pregnancy on serum thyroglobulin and detection of recurrent disease shortly after delivery in thyroid cancer survivors. *Thyroid*, **17**, 543–547.
26 Rosario, P.W., Barroso, A.L. & Purisch, S. (2007) The effect of subsequent pregnancy on patients with thyroid carcinoma apparently free of the disease. *Thyroid*, **17**, 1175–1176.

CHAPTER 15

15 Thyroid cancer in childhood

Differentiated thyroid cancer (DTC) is rare in children, the presentation and options for treatment have been extensively reviewed.[1,2] 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 the threshold for surgical excision is lower than in adults. Papillary thyroid cancer (PTC) in children aged 15 years or less is more aggressive than in adults, with a high prevalence of gross lymph node metastases at presentation. Lymph node involvement is found in up to 90%, the risk of recurrent disease is higher than adults.[3–5] However, disease specific mortality even in young patients with lung metastases is very low.[6] Follicular thyroid cancer in children and adolescents up to 20 years of age is very rare (1.9% of patients with follicular cancer), outcomes from treatment are similar to those in adult patients.[7]

i The general principles of management are similar to those in adults; however, the specialist team must include a paediatric endocrinologist, paediatric oncologist (or nuclear medicine physician) and nurse specialist or counselor.
Good Practice Point ☑

ii The Manual of Cancer Services and Current Peer Review standards[8] require that: For each patient in the Teenage and Young Adult (TYA) age group (19–24 years), the (Thyroid Cancer) MDT should agree treatment decisions with the TYA MDT
National Cancer Peer Review Programme, measure 11-2I-148

iii As the risks of complications from thyroidectomy are higher in young patients[9] it is recommended that patients are treated by nominated members of an adult thyroid cancer MDT or 'high volume' paediatric thyroid surgeon.
Good Practice Point ☑

iv Patients with PTC should be considered for total thyroidectomy and central compartment lymph node dissection to reduce the risk of local recurrence **(3, D).**

v The surgical treatment of children/adolescents with follicular thyroid cancer is as recommended for adult patients (Chapter 7.6) **(3, D).**

vi Patients with clinically/radiological involvement of cervical lymph nodes should undergo central/selective lateral neck dissection as recommended for adult patients (Chapter 7.6).

vii TSH suppression[10] is recommended for most patients[10] **(4, D).**

viii Radioiodine remnant ablation (RRA)[4,10–12] is recommended for all children particularly those aged under 10 years, but the decision about RRA should be individually determined **(4, D).**

ix Follow-up with serial serum thyroglobulin (Tg) measurements should be lifelong[13] **(2−, D).**

The treatment of MTC in children is discussed in Chapter 17.

References

1 Rivkees, S.A., Mazzaferri, E.L., Verburg, F.A. *et al.* (2011) The treatment of differentiated thyroid cancer in children: emphasis on surgical approach and radioactive iodine therapy. *Endocrine Reviews*, **32**, 798–826.

2 Jarzab, B., Handkiewicz-Junak, D. & Wloch, J. (2005) Juvenile differentiated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review. *Endocrine-Related Cancer*, **12**, 773–803.

3 Hay, I.D., Gonzalez-Losada, T., Reinalda, M.S. *et al.* (2010) Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. *World Journal of Surgery*, **34**, 1192–1202.

4 Jarzab, B., Handkiewicz Junak, D., Wloch, J. *et al.* (2000) Multivariate analysis of prognostic factors for differentiated thyroid carcinoma in children. *European Journal of Nuclear Medicine*, **27**, 833–841.

5 Grigsby, P.W., Gal-or, A., Michalski, J.M. *et al.* (2002) Childhood and adolescent thyroid carcinoma. *Cancer*, **95**, 724–729.

6 Pawelczak, M., David, R., Franklin, B. *et al.* (2010) Outcomes of children and adolescents with well-differentiated thyroid carcinoma and pulmonary metastases following ^{131}I treatment: a systematic review. *Thyroid*, **20**, 1095–1101.

7 Enomoto, K., Enomoto, Y., Uchino, S. *et al.* (2013) Follicular thyroid cancer in children and adolescents: clinicopathologic features, long-term survival, and risk factors for recurrence. *Endocrine Journal*, **60**, 629–635.

8 National Cancer Peer Review – National Cancer Action Team. Manual for Cancer Services: Head and Neck Measures Version 3.0. Available from: http://www.mycancertreatment.nhs.uk/wp-content/themes/mct/uploads/2012/09/resources_measures_HeadNeck_April2013.pdf (accessed 12 June 2014).

9 Sosa, J.A., Tuggle, C.T., Wang, T.S. *et al.* (2008) Clinical and economic outcomes of thyroid and parathyroid surgery in children. *Journal of Clinical Endocrinology and Metabolism*, **93**, 3058–3065.

10 Spoudeas H.A. (ed) (2005) Paediatric endocrine tumours. A multi-disciplinary consensus statement of best practice from a working group convened under the auspices of the BSPED and UKCCSG. Novo Nordisk, Crawley.

11 Thompson, G.B. & Hay, I.D. (2004) Current strategies for surgical management and adjuvant treatment of childhood papillary thyroid carcinoma. *World Journal of Surgery*, **28**, 1187–1198.

12 La Quaglia, M.P., Black, T., Holcomb, G.W. *et al.* (2000) Differentiated thyroid cancer: clinical characteristics, treatment, and outcome in patients under 21 years of age who present with distant metastases. A report from the Surgical Discipline Committee of the Children's Cancer Group. *Journal of Pediatric Surgery*, **35**, 955–959.

13 Landau, D., Vini, L., Hern, R.A. *et al.* (2000) Thyroid cancer in children: the Royal Marsden Hospital experience. *European Journal of Cancer*, **36**, 214–220.

CHAPTER 16

16 Pathology reporting, grading and staging of thyroid cancers

16.1. General principles

A general approach to specimen handling is outlined below. Points specifically relating to medullary carcinoma are discussed in Chapter 17. Most lesions should have had fine-needle aspiration cytology (FNAC) before surgery (Chapter 5) so at least a differential diagnosis should be available. Inter-observer variation is documented in thyroid tumour histology[1] and the range of prognostic features can require experience in their recognition.[2] A careful, accurate and thorough histopathology report is essential because many of the histological features affect staging and prognosis and may therefore influence clinical management decisions.

i Histopathologists reporting thyroid tumours should have a special interest in thyroid pathology or participate in a network with the opportunity of pathology review **(2+, C)**.
Key recommendation

ii A nominated pathologist should be a core member of the local thyroid cancer Multidisciplinary Team (MDT).
National Cancer Peer Review Programme, measure 11-2I-101[3]

iii Cases should be handled and reported according to the current dataset of the Royal College of Pathologists (RCPath) 2014[4] **(4, D).**
Key recommendation

iv Intra-operative frozen section may occasionally be used to confirm the diagnosis of papillary thyroid carcinoma, or to confirm lymph node involvement, but should not be used to differentiate follicular carcinoma from adenoma[5] **(2−, D).**

v Encapsulated follicular-patterned lesions should be widely sampled at the interface between the tumour, its capsule and the normal gland to detect capsular (tumour capsule) or vascular invasion (angioinvasion). Small lesions (≤30 mm in maximum dimension) should be processed in their entirety and at least 10 blocks should be taken from larger lesions **(4, D).**

vi Lymph nodes should be carefully dissected, the number counted and locations noted if possible. Ipsilateral, midline and contralateral nodes should be documented separately. Formal neck dissections should be dealt with according to RCPath protocols for head and neck cancers[6] **(4, D).**

16.2. Pathology report

The core data set shown in Table 16.1 should be included **(4, D).**

16.3. Pathological staging

i Pathological staging should be performed using the 7th edition of the TNM classification[7] **(4, D).**
Key recommendation

ii In multifocal lesions, the largest is used for staging purposes **(4, D).**

16.4. Staging protocol

See Chapter 2.

16.5. Summary of thyroid cancer types

There are many different types of thyroid carcinoma and the type should be clearly stated in the pathology report. In summary, the main types are given below and more information is available in standard endocrine pathology texts and the RCPath Dataset[4]:

Papillary Thyroid Carcinoma (PTC). This is derived from the follicular epithelial cells and is the commonest cancer type. There are many variants (e.g. classical, cystic, follicular, solid, cribrifommorular, oncocytic, diffuse sclerosing, tall cell, columnar cell) some of which have prognostic implications (e.g. tall cell and columnar cell variants are said to have a worse prognosis).

Follicular Variant of Papillary Thyroid Carcinoma (FVPTC). Warrants special mention. There are three types:

a) *Non-encapsulated or infiltrative.* The clinical behavior and molecular genetics are similar to classical PTC.
b) *Encapsulated.* The clinical behavior and molecular genetics are more like those of follicular neoplasms, and need assessment in a similar way:
   a. *Encapsulated non-invasive FVPTC.* There is no/a very low risk of recurrence or metastasis, and lobectomy may be sufficient treatment (Chapter 7.6).
   b. *Encapsulated FVPTC with capsular and/or vascular invasion.* Capsular invasion alone does not seem to adversely affect outcome and hemithyroidectomy alone may be sufficient treatment (Chapter 7.6). Vascular (angio)invasion is required for behaviour as a low grade malignancy.
c) *Diffuse/aggressive/multinodular.* This is rare, occurs typically in younger patients and has a worse prognosis.

Papillary microcarcinoma (microPTC). A microcarcinoma is up to and including 10 mm in greatest dimension. These are more fully discussed in Chapter 8.

Follicular carcinoma. This is also derived from the follicular epithelial cells.

a) *Minimally invasive follicular carcinoma.* This is a single encapsulated nodule in which invasion has been found histo-

Table 16.1. Histopathology reporting proforma for thyroid cancer

Surname……	Forenames……..… Sex.....	Date of birth…….....
Hospital…….…….……	Hospital no…….….....	NHS/CHI no……..
Date of receipt…….……	Date of reporting…….….....	Report no…….....
Pathologist…….……....	Surgeon…….……	

CORE DATA ITEMS

Specimen type

Total thyroidectomy	☐
Left hemithyroidectomy	☐
Right hemithyroidectomy	☐
Isthmusectomy	☐
Biopsy of thyroid	☐
Biopsy/resection of metastasis	☐ (Define site……)
Additional specimens, e.g. lymph node dissection	☐ (Specify..……)

Location of carcinoma

Left lobe ☐ Right lobe ☐ Isthmus ☐ Other ☐ (Specify.....)

No of tumours ..... Single ☐ Multiple (m) ☐ Bilateral (m) ☐

Size.....mm (of largest if multiple)

Cancer type

Papillary carcinoma ☐

Classical PTC ☐

FVPTC ☐

- Encapsulated FVPTC ☐
  - Non-invasive ☐
  - Capsular invasion only ☐
  - Vascular (angio)invasion — Present ☐ Not identified ☐ Uncertain ☐ Cannot be assessed ☐
- Non-encapsulated FVPTC ☐
- Diffuse / aggressive / multinodular FVPTC ☐

Microcarcinoma (pT1a):

- Single ☐ Multiple (m) ☐ Bilateral (m) ☐
- Desmoplastic fibrosis or infiltrative growth pattern present ☐
- Incidental finding ☐

Other PTC variant ☐ (Specify.....)

Oncocytic variant — Yes ☐ No ☐

Minority poorly differentiated (not anaplastic) component — Yes ☐ No ☐

Follicular carcinoma ☐

Minimally invasive ☐

- Capsular invasion only ☐
- Vascular (angio)invasion — Present ☐ Not identified ☐ Uncertain ☐ Cannot be assessed ☐

Widely invasive ☐

- Vascular (angio)invasion — Present ☐ Not identified ☐ Uncertain ☐ Cannot be assessed ☐

Oncocytic variant Yes ☐ No ☐

Minority poorly differentiated (not anaplastic) component Yes ☐ No ☐

Medullary carcinoma ☐

Poorly differentiated carcinoma (majority (> 50%) of tumour is poorly differentiated) ☐
Differentiated component identified ☐ (Specify)…….....

Undifferentiated/anaplastic carcinoma ☐
Differentiated component identified ☐ (Specify)…….....

Mixed medullary carcinoma with papillary carcinoma ☐
Mixed medullary carcinoma with follicular carcinoma ☐

Angioinvasion / vascular invasion Present ☐ Not identified ☐
Uncertain ☐ Cannot be assessed ☐

Extent

Confined to thyroid (intrathyroidal) ☐

Minimal extrathyroidal extension (seen by microscopy) beyond thyroid capsule into sternothyroid or perithyroidal soft tissues only (pT3) ☐

Tumour invades beyond thyroid capsule into subcutaneous soft tissues, larynx, trachea, oesophagus or recurrent laryngeal nerve; or an anaplastic carcinoma not extending beyond the thyroid capsule (pT4a) ☐

Tumour invades beyond thyroid capsule into prevertebral fascia, mediastinal vessels or encasement of carotid artery, or anaplastic carcinoma extending beyond thyroid capsule (pT4b) ☐

Excision margins

Free of tumour (R0) ☐ Minimum distance .....mm

Microscopic tumour at margin (R1) ☐

Macroscopic tumour at margin (R2) ☐

Lymph nodes

Total number of lymph nodes identified.....

Level VI lymph nodes ☐ Total number ..... Number positive ..... (pN1a)

Other lymph nodes ☐ (Specify site .....)
Total number ..... Number positive ..... (pN1b)

Distant metastasis

Pathological confirmation (pM1) ☐ (Specify site .....)

Stage pT ……. pN ……. pM ……. R …….

SNOMED code TB6 M…….

Signature ……..…. Date……..……

logically in the region of the tumour capsule. This is why a distinction cannot be made cytologically between follicular adenoma (no invasion) and follicular carcinoma.

a. *With capsular invasion only*. These have a minimal risk of metastasis.
b. *With vascular (angio)invasion* (with or without capsular invasion). These may develop blood borne metastatic disease.

b) *Widely invasive follicular carcinoma*. This shows gross invasion or extensive microscopic infiltration. The prognosis is worse than the minimally invasive tumour.

Oncocytic (Hurthle cell) tumours. Oncocytic change can occur in any thyroid tumour type, benign or malignant, though is most often associated with follicular neoplasms. Assessment of tumour type is the same as for the non-oncocytic version.

'Differentiated Thyroid carcinoma' (DTC). This term relates collectively to PTC and follicular carcinomas.

Poorly differentiated carcinoma (PDC). These tumours are derived from follicular epithelial cells and have a level of differentiation between DTC and anaplastic thyroid cancer

(ATC). The term is used when the majority (>50%) of the tumour is of this type. The behavior is then worse than for DTCs. 'Insular' carcinoma is one example of PDC. Areas of pre-existing DTC may be seen in a PDC. Smaller foci of poor differentiation may be seen in otherwise differentiated carcinomas, and should be documented because they may carry prognostic implications between those of DTC and PDC.

Anaplastic (undifferentiated) carcinoma (ATC). These tumours show no differentiation. The term is used when any amount of the tumour has this appearance. They are discussed in full in Chapter 18.

Medullary thyroid carcinoma (MTC). This tumour derives from the calcitonin-producing C cells of the thyroid. It is discussed in full in Chapter 17.

Lymphoma. These are nearly always of non-Hodgkin's type, and may be low or high grade. There is often pre-existing Hashimoto's thyroiditis.

References

1 Elsheikh, T.M., Asa, S.L., Chan, J.K. *et al.* (2008) Interobserver and intraobserver variation among experts in the diagnosis of thyroid follicular lesions with borderline nuclear features of papillary carcinoma. *American Journal of Clinical Pathology*, **130**, 736–744.

2 Stephenson, T.J. (2006) Prognostic and predictive factors in endocrine neoplasia. *Histopathology* **48**, 629–643.

3 http://www.mycancertreatment.nhs.uk/wp-content/themes/mct/uploads/2012/09/resources_measures_HeadNeck_April2013.pdf (accessed 12 June 2014).

4 Royal College of Pathologists. Dataset for thyroid cancer histopathology reports. http://www.rcpath.org/NR/rdonlyres/19E175B5-9638-483A-8088-A18DB50BEC4A/0/G098_DRAFTThyroidDataset_Nov13.pdf

5 Osamura, R.Y. & Hunt, J.L. (2008) Current practices in performing frozen sections for thyroid and parathyroid pathology. *Virchows Archiv* **453**, 433–440.

6 Royal College of Pathologists (2011) Dataset for Histopathology Reporting of Nodal Excisions and Neck Dissection Specimens Associated with Head and Neck Carcinomas, 3rd edn. The Royal College of Pathologists, London.

7 Sobin, L.H., Gospodarowicz, M.K. & Wittekind, C. (2009) TNM Classification of Malignant Tumours, 7th edn. Wiley-Blackwell, Oxford.

CHAPTER 17

17 Medullary thyroid cancer

Medullary thyroid cancer (MTC) is a rare disease accounting for approximately 3% (adult) to 10% (paediatric) of thyroid cancers and requires treatment from a multidisciplinary regional service.

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

- Twenty-five per cent of MTC is familial (multiple endocrine neoplasia 2 (MEN2), MEN3 (formerly MEN2B), and inherited in an autosomal dominant manner necessitating a comprehensive and integrated approach to the patient and their family. Developments in the molecular genetics of MTC have facilitated a rational framework for clinical care that requires specific application in individual patients and their families in conjunction with the cancer genetics service
- When MTC arises as part of a familial syndrome, assessment and management of the other endocrine tumours are required
- Patients may survive for many years even with a significant tumour burden, although the prognosis is poorer than differentiated cancer (Table 17.1). This makes the risk/benefit decisions for additional intervention for persistent or recurrent disease difficult

i All patients with or, at risk of MTC should be referred for investigation/surgical treatment to a cancer centre[2] **(4, D).**
Key recommendation

ii Clinical services for MTC should dovetail with those for MEN1 and MEN2, which require similar services and raise common issues **(4, D).**

17.1. Presentation

MTC may present with a neck mass, symptoms related to pressure effects (dysphagia, dysphonia) or with distant metastasis. In addition, patients with extensive MTC may present with frequent loose stools and vasomotor flushing that result from coincident secretion of peptides. Less commonly, adrenocorticotrophin (ACTH) is secreted.

The diagnosis may be made following fine-needle aspiration cytology (FNAC) of a thyroid nodule or lymph node in the absence of previous clinical suspicion. Unsuspected MTC can also be found at/after surgery.

i In all cases, a comprehensive family history must be taken to include first- and second-degree relatives to search for features of MTC or other endocrinopathies that may occur in individuals with familial MTC. This includes a history of unexpected sudden death, which should raise the suspicion of occult phaeochromocytoma **(4, D).**
Key recommendation

Calcitonin screening of patients with thyroid nodules. Controversy still exists with regard to the use of routine calcitonin measurement in patients with nodular thyroid disease (see also Appendix 1.2). Historically, the American Thyroid Association (ATA) MTC guidelines (2009)[3] and European Thyroid Association (ETA) consensus (2006)[4] have been at variance on this matter. A review article in 2009 stated 'more evidence is needed before routine calcitonin screening can be recommended in the initial management of thyroid nodular disease'[5].

Although basal calcitonin concentrations >60 ng/l[6] to 100 ng/l[7] are described as highly suggestive/pathognomonic of MTC, diagnostic uncertainty exists at lower concentrations of calcitonin consequent to the potential confounding effects of:

- Assay related factors (e.g. Hook effect, inter-laboratory variation in normal range, heterophilic antibodies)
- Drugs (e.g. proton pump inhibitors)
- Co-existing disease states [e.g. hypercalcaemia, renal failure, neuroendocrine tumours, lymphocytic thyroiditis, papillary thyroid cancer (PTC)]
- Sporadic C-cell hyperplasia
- Other (gender specific differences, smoking)

Calcitonin stimulation tests (with pentagastrin or calcium) are required to confirm or refute the need for thyroid surgery in patients with calcitonin values that are 'mildly' elevated, although the exact cut-off values at which further investigation is necessary remain to be clearly defined. Pentagastrin-stimulated calcitonin values >250 ng/l in women and 500 ng/l in men are increasingly predictive of MTC[6–8] but there is uncertainty as to the validity of these values when calcium stimulation has been performed.[9] In addition, pentagastrin is not freely available.

Protagonists of calcitonin screening state the benefits of early diagnosis, one step surgery and a greater potential for cure. Those against quote the lack of cost effectiveness data to support its use and as yet the absence of reported benefit in terms of long-term outcome. In contrast, the argument that the natural history of 'occult' MTC is unknown seems unsupported by the evidence in that that even sporadic micro MTC have a high rate of lymph node metastasis – up to 20% cases <5 mm tumour diameter and up to 43% up to 10 mm.[10]

i At the present time there is insufficient evidence on which to recommend routine calcitonin screening in patients with nodular thyroid disease **(4, D).**

Table 17.1. Medullary thyroid carcinoma staging[1]

	10-year survival (%)
Stage I	
pT1, N0, M0	100
Stage II	
pT2, N0, M0	93
pT3, N0, M0	
pT4, N0, M0	
Stage III	
Any pT, N1, M0	71
Stage IV	
Any pT, any N, M1	21

17.2. Initial investigations of patients with suspected or confirmed MTC

Ultrasound (US), fine-needle aspiration cytology (FNAC) and biochemical investigations.

i The initial evaluation of patients with suspected MTC includes US of the thyroid, FNAC and a baseline value for calcitonin, which may confirm the diagnosis and can indicate the likelihood of remission and extent of disease[11–14] (Appendix 1.2) **(2+, C)**.
Key recommendation

Once the diagnosis of MTC is confirmed, the following additional investigations should be performed:

i In all cases at least one 24-h urine sample assayed for catecholamines and nor/metanephrines or plasma nor/metanephrines is required to exclude phaeochromocytoma, and a serum calcium to exclude hyperparathyroidism. These tests must be performed in all MTC patients prior to neck surgery even in the absence of a positive family history or symptoms **(4, D)**.
Key recommendation

ii Neck CT/MRI is indicated if there is suspicion of locally advanced disease **(4, D).**

iii A stimulation test with calcium/pentagastrin may rarely be indicated to confirm a diagnosis of MTC in relatives of patients with gene negative inherited MTC (<5%),[15] or to exclude causes of false-positive basal calcitonin elevation,[5] especially when calcitonin levels are only mildly elevated. Pentagastrin availability is limited and if utilised, the test should take place in a specialist endocrine centre **(4, D).**

iv Patients with a new diagnosis of MTC will require support from the clinical team and access to good quality information (Appendix 4, Patient Information Leaflet 5).
Good Practice Point ☑

Pre-operative staging. The identification of metastatic MTC prior to first time surgery will explain persistent post-operative calcitonin elevation. In most patients, positive findings will not alter the indication for surgical intervention in the neck, but may alter the extent of cervico-mediastinal surgery. In previously untreated patients with node positive MTC, tumour diameter of 12–15 mm or calcitonin concentrations of >400 ng/l predict an increased risk of metastatic disease with a cumulative risk of >50% if calcitonin concentrations are >15000 ng/l.[12] Chest CT, liver MRI and bone scintigraphy/MRI axial skeleton are the most efficient means to detect systemic disease.[16] In patients with MTC, systemic staging is indicated in node positive patients with calcitonin levels >400 ng/l[17] **(4, D).**

i CT chest, dual phase CT liver or MRI,[17] bone scintigraphy or MRI spine are recommended for systemic staging[18] **(4, D).**

ii ^{18}fluoro-deoxy-glucose (FDG)-positron emission tomography (PET)-CT (FDG PET-CT) is not recommended prior to first time surgery **(4, D).**

Genetic testing.

i In all confirmed cased of MTC, *RET* mutation analysis to establish the possible genetic basis for the disease within an individual or kindred, should be performed even in the absence of a positive family history.
Good Practice Point ☑
Key recommendation

17.3. Treatment

Prior to thyroid surgery all patients should be managed as described in Chapter 7.3.

Surgery. The aims of first-time surgical treatment of MTC are loco-regional control (the neck and superior mediastinum), and in some patients biochemical as well as clinical cure.[14,19]

i Patients with established MTC should undergo a minimum of total thyroidectomy and central compartment node dissection, the inferior limit of the dissection being the inominate artery (levels VI and VII)[14] **(2+, C).**
Key recommendation

ii In patients with incidental, sporadic (*RET* negative), unifocal micro MTC <5 mm, completion thyroidectomy is not essential,[10,20] but approximately 20% of patients may have node metastases.[10,21] Post-operative basal calcitonin should determine the need for further surgery (completion thyroidectomy/central neck dissection) **(2+, C).**

iii Patients with clinical or radiologically involved lymph nodes in the lateral compartment should in addition to total thyroidectomy and central neck dissection undergo selective lateral neck dissection of levels IIa–Vb.
Good Practice Point ☑

iv Ipsilateral prophylactic lateral neck dissection is recommended in the presence of central compartment node metastases on the basis that the risk of lateral node involvement is at least 70%[22] **(3, D).**

v As preoperative imaging of the central compartment has a low sensitivity for detection of lymph node metastases, the need for prophylactic ipsilateral lateral compartment lymph node dissection may not be apparent without

histopathological confirmation of involved lymph nodes. **Personalised Decision Making** is recommended based upon the probability of central compartment nodal metastases (tumour size/basal calcitonin)[14] with the options of (a) central and ipsilateral compartment lymph node dissection at initial surgery, (b) central compartment lymph node dissection with intraoperative frozen section (c) a two stage procedure **(4, D).**

The need for prophylactic bilateral lateral compartment node dissection in the presence of central compartment node metastases is unclear. Approximately 35% patients with central compartment node metastases will have contralateral lateral compartment node metastases,[23] and bilateral lateral neck dissection in patients with basal calcitonin of ≤1000 ng/l will achieve biochemical cure in more than 50% of patients.[14] However, the likelihood of biochemical cure is much reduced in patients with more than 10 nodal metastases or more than 2 lymph node compartments involved.[22] In summary, bilateral prophylactic lateral neck dissection will likely reduce calcitonin levels and the need for reoperation, but its impact on survival for many patients is less certain.

i In the absence of clinical or radiological evidence of central and ipsilateral lateral node metastases, dissection of the contralateral lateral neck is not recommended **(4, D).**
ii In the absence of direct invasion, the sternomastoid muscle/internal jugular vein/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 **(4, D).**
iii The management of recurrent laryngeal nerve involvement by tumour is as described in Chapter 7.4.
iv When there is strong suspicion or evidence of mediastinal node involvement below the brachiocephalic vein, and no evidence of distant metastases, the patient should be considered for further surgery[24,25] **(3, D).** This will require a sternotomy.
v 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 **(3, D).**

Prophylactic surgery RET gene mutation carriers. Prophylactic thyroidectomy has dramatically improved outcomes in patients with MEN2 and MEN3 (MEN2B), such that about 90% of young patients with *RET* mutations who had a prophylactic thyroidectomy have no evidence of persistent or recurrent MTC at 7 years after surgery. In contrast the 10-year survival for patients with metastatic MTC is about 20%.[26]

i Prophylactic surgery should be offered to *disease-free* carriers of germ line *RET* mutations, identified by genetic screening.[27–31] The possibility of future surgery should be discussed with parents before testing children. In ideal circumstances these individuals 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. This will depend upon the genotype and the age of the patient. Basal calcitonin levels indicate the likelihood of MTC ± node metastases.[32] It is important to distinguish the need for therapeutic surgery from prophylactic surgery.

Good Practice Point ☑

Key recommendation

ii Children with MEN 3 (MEN2B) should undergo prophylactic thyroidectomy preferably within the first 6 months but within the first year of life[33,34] **(2+, C).**
iii Children with MEN 2A associated with a 634 codon mutation should undergo thyroidectomy before the age of 5 years[31] **(2+, C).**
iv Prophylactic surgery for MEN 2A gene carriers with other than 634 codon mutations or FMTC, may be delayed, beyond the age of 5 years, provided that the basal calcitonin remains within the normal range, according to the risk stratifications and recommendations stated in the American Thyroid Association (ATA) MTC Guidelines[3] (Tables 17.2 and 17.3) **(2+, C).**
v The requirement for lymph node dissection at the time of 'prophylactic' thyroidectomy should be considered in gene carriers based upon the basal calcitonin level. The risk of lymph node metastases is very low in patients with only mildly/moderately elevated basal calcitonin concentrations (proposed cut-offs in different series: 20 ng/l[14], <31 ng/l[30], 60 ng/l,[32] 90 ng/l)[13] **(2+, C).**
vi Gene carriers with 'late' presentation and established MTC as defined by clinical presentation, cross sectional imaging and/or significantly elevated calcitonin levels should be treated as outlined in Section 17.3.

Post-operative management.

i Following surgery, voice dysfunction and hypocalcaemia should be managed as described in Chapter 11.1 and 11.2.
ii After total thyroidectomy patients should be given thyroxine at a replacement dose aiming for a normal serum TSH **(4, D).**

17.4. Adjuvant therapies

Unlike differentiated thyroid cancer (DTC), radioiodine ablation or therapy are not options. Routine adjuvant external beam radiotherapy (EBRT) has not been shown to improve survival.[35,36]

i EBRT should be considered only once optimal surgery has been performed and if there is significant risk of local recurrence. This maybe where there is macroscopic residual disease or microscopic residual disease on the background of large volume disease[37] **(4, D).**
ii EBRT should not be used to consolidate inadequate surgery **(4, D).**

Table 17.2. Genotype–Phenotype correlations and risk levels for aggressive medullary thyroid cancer (adopted from[3] with permission from the American Thyroid Association)

Mutation	Exon	ATA risk level[a]	MTC risk level[b]	FMTC[d]	MEN 2A[c]					MEN 2B[c]		References
					MTC	PHPT	PHEO	CLA	HSCR	MTC	PHEO	
G321R[e]	5	A		+	MA	–	–	–	–	–	–	(100)
531/9 base pair duplication	8	A		+	MA	–	–	–	–	–	–	(364)
532 duplication[e]	8	A		+	?	–	–	–	–	–	–	(177)
C515S[e]	8	A		+	MA	–	–	–	–	–	–	(365)
G533C	8	A		+	MA	–	R	–	–	–	–	(99, 366–368)
R600Q[e]	10	A		+	MI	–	–	–	–	–	–	(369)
K603E[e]	10	A		+	MI	–	–	–	–	–	–	(370)
Y606C[e]	10	A		+	?	–	–	–	–	–	–	(371, 372)
C609F/R/G/S/Y	10	B	1	+	MA	MI	R	–	+	–	–	(14, 46, 85, 373–375)
C611R/G/F/S/W/Y	10	B	2	+	MA	MI	R	–	+	–	–	(46, 85)
C618R/G/F/S/Y	10	B	2	+	MA	MI	MI	–	+	–	–	(46, 85)
C620R/G/F/S/W/Y	10	B	2	+	MA	MI	MI	–	+	–	–	(46, 85, 374)
C630R/F/S/Y	11	B		+	MA	R	R	–	–	–	–	(73, 376, 377)
D631Y[e]	11	B		+	?	–	–	–	–	–	–	(378)
633/9 base pair duplication	11	B		+	MA	MI	MI	–	–	–	–	(379)
C634R	11	C	2	–	MA	MI	MA	+	–	–	–	(46, 85, 380, 381)
C634G/F/S/W/Y	11	C	2	+	MA	MI	MA	+	–	–	–	(46, 85, 380–382)
634/12 base pair duplication	11	B		+	MA	MI	–	–	–	–	–	(383)
635/insertion ELCR;T636P	11	A		+	MA	–	–	–	–	–	–	(371)
S649L	11	A		+	MI	R	–	–	–	–	–	(14, 124, 384, 385)
K666E[e]	11	A		+	MI/MA	–	MI	–	–	–	–	(371)
E768D	13	A	1	+	MA	R	R	–	–	–	–	(46, 73, 90, 378)
N777S[e]	13	A		+	MI	–	–	–	–	–	–	(386)
L790F	13	A	1	+	MA	R	R/MI	–	–	–	–	(86, 378)
Y791F	13	A	1	+	MA	MI	MI	–	–	–	–	(86, 378, 387)
V804L	14	A	1	+	MA	MI	R	–	–	–	–	(46, 86, 388)
V804M	14	A	1	+	MA	R	R	–	–	–	–	(46, 86, 388, 389)
V804M + V778I[f]	13/14	B		+	MA	–	–	–	–	–	–	(390)
V804M + E805K	14	D		–	–	–	–	–	–	MA	MA	(71)
V804M + Y806C	14	D		–	–	–	–	–	–	MA	MA	(72–74)
V804MþS904C[g]	14/15	D		–	–	MI	–	–	–	MA	–	(101)
G819K[e]	14	A		+	?	–	–	–	–	–	–	(14)
R833C[e]	14	A		+	?	–	–	–	–	–	–	(391)
R844Q[e]	14	A		+	?	–	–	–	–	–	–	(14, 378)
R866W[e]	15	A		+	MA	–	–	–	–	–	–	(392)
A883F	15	D	3	–	–	–	–	–	–	MA	MA	(393, 394)
S891A	15	A	1	+	MA	R	R	–	–	–	–	(14, 395–397)
R912P	16	A		+	MI	–	–	–	–	–	–	(14, 398)
M918T	16	D		–	–	–	–	–	–	MA	MA	(46)

[a]Risk from aggressive MTC: level D is highest risk.
[b]Risk from aggressive MTC from the Seventh International Workshop on MEN (2): level 1, high risk; level 2, higher risk; level 3, highest risk.
[c]Organ-specific penetrance: MA, majority; MI, minority; R, rare.
[d]Presence (+) of inherited MTC in the absence of PHPT or PHEO has been described, although the number of family members and number of family generations studied and duration of follow-up is variable. Historically, mutations initially considered diagnostic of FMTC have eventually demonstrated some penetrance of the MEN 2A phenotype. The absence (−) of association with FMTC indicates that inheritance of MTC in isolation is very unlikely.
[e]Mutations based on limited families = case reports and may represent variants of unknown significance.
[f]Phenotype associated with corneal nerve thickening. gPhenotype associated with mucosal neurilemmomas.
[g]Phenotype associated with mucosal neurilemmomas.

17.5. Pathology

The general principles for specimen handling, macroscopic description and microscopic reporting should follow the Royal College of Pathologists' dataset[38,39] and are outlined in Chapter 16. For cases of MTC, block selection from the thyroid should be sufficient to confirm the diagnosis, recognise the relationship to the thyroid capsule, and identify any extra-thyroidal spread with definition of the tissues invaded.

Table 17.3. American thyroid association risk level and prophylactic thyroidectomy testing and therapy (adopted from[3] with permission from the American Thyroid Association)

ATA risk level	Age of RET testing	Age of required first US	Age of required vfirst serum C_t	Age of prophylactic surgery
D	ASAP and within the 1st year of life	ASAP and within the 1st year of life	6 months, if surgery not already done	ASAP and within the first year of life
C	<3–5 years	>3–5 years	>3–5 years	Before age 5 years
B	<3–5 years	>3–5 years	>3–5 years	Consider surgery before age 5. May delay surgery beyond age 5 years if stringent criteria are met[a]
A	<3–5 years	>3–5 years	>3–5 years	May delay surgery beyond age 5 years if stringent criteria are met[a]

[a]A normal annual basal ± stimulated* serum C_t, normal annual neck US, less aggressive MTC family history, and family preference. ASAP, as soon as possible.

i The identification of C cell hyperplasia (CCH) can be difficult and is best done with calcitonin immuno-confirmation in areas of thyroid distant to the main tumour[39] **(4, D).**

ii Histologically, it is recommended that the diagnosis of MTC is confirmed by calcitonin immunoreactivity **(4, D).**

iii Prophylactic thyroidectomy specimens should be sampled in total and calcitonin immunoreactivity used for lesions suspected of being CCH or MTC **(4, D).**

Tumour staging. The TNM system (Table 2.1) should be applied **(4, D)**. Age is not a prognostic factor in MTC. Staging for MTC is shown in Table 17.1.

17.6. Follow-up of MTC

i Lifelong follow-up is recommended **(4, D).**

Key recommendation

ii Postoperatively, calcitonin should be measured no earlier than 15 days after thyroidectomy and may take more than 2 months to fall to the lowest level.[40,41] Response to primary surgery can be assessed clinically and by the measurement of serum calcitonin and carcinembryonic antigen (CEA) usually 6 months after surgery[42] **(4, D).**

iii The presence of an elevated but stable calcitonin level postoperatively may be managed conservatively, provided treatable disease has been excluded radiologically. Progressively rising calcitonin concentration should trigger imaging for further staging. Follow-up intervals should be judged individually based on disease behavior and levels of doubling times of tumour markers **(4, D).**

iv Calcitonin and CEA doubling times correlate with tumour progression and are useful prognostic indicators for MTC recurrence and survival.[42] At least four calcitonin/CEA values are required to calculate doubling time (and should be estimated (Appendix 1.2). An on-line calculator is available.[43] Calcitonin and CEA doubling times are recommended **(1+, A).**

17.7. Investigation of persistent or increasing hypercalcitoninaemia in treated patients

Elevated calcitonin concentrations after surgery are a common finding. This will depend upon the pre-operative basal calcitonin and the stage of the tumour at presentation.[11,44] The clinical team should consider for each patient the opportunity for biochemical cure, the prognosis, the risk of local relapse, as well as the potential morbidity from further surgery. The commonest sites of persistent/metastatic disease are neck, mediastinum, lungs, liver and bone.

i The decision to investigate patients with persistent or increasing hypercalcitonaemia should be made on a case by case basis **(4, D).**

ii The clinical features and likely anatomical site of recurrent or metastatic disease should guide the choice and sequence of imaging **(4, D)**.

Initial imaging for persistent or increasing hypercalcitoninaemia.

i Initial cross-sectional imaging for recurrent or metastatic disease should include a neck US, CT neck and chest with contrast, and either dual phase CT liver or MRI liver. MRI provides better sensitivity for detection of liver metastases[18] **(4, D).**

ii Whole body and tomographic (SPECT-CT) imaging using ^{123}I meta-iodobenzylguanidine (mIBG), ^{111}In somatostatin analogues and ^{99m}Tc pentavalent dimercaptosuccinic acid [DMSA(V)] may be useful for the investigation of occult disease when other imaging modalities have failed **(4, D).**

Additional imaging for persistent or increasing hypecalcitoninaemia. ^{18}F fluorodeoxygucose (FDG) PET-CT imaging may be helpful in restaging patients with aggressive disease associated with rapidly rising tumour markers,[45] particularly where calcitonin >1000 ng/l.[46] ^{18}F-dihydroxyphenylalanine (F-DOPA) PET-CT has a higher sensitivity (~80%)[47] for the investigation of recurrent MTC, but availability is limited in the UK. PET-CT

using ^{68}Ga-labelled somatostatin analogues is less sensitive (33%) than F-DOPA[45] and access is similarly limited in the UK.

i The following nuclear imaging scans are recommended for investigation of postoperative hypercalcitoninaemia when US, CT or MRI are unhelpful **(4, D):**

- ^{99m}Tc methylene diphosphonate (MDP) bone scintigraphy
- FDG PET-CT
- Consider ^{111}In octreotide or ^{68}Ga DOTATATE PET-CT

17.8. Treatment of persistent or recurrent disease

It is important to distinguish loco-regional, persistent/recurrent disease from distant micro- or macro-metastases as the cause of an elevated calcitonin. True local recurrence is unusual after adequate initial surgery. Re-operation is reported to provide long-term disease eradication in at least one third of patients.[48]

Surgery.

i When initial surgery has been incomplete, re-operation on the neck (lymphadenectomy of the central and/or lateral compartments) with curative intent should be considered particularly when basal calcitonin concentration is <1000 ng/l and 5 or fewer disease positive nodes were removed at previous surgery and in the absence of extra-thyroidal spread[49] **(2++, B).**

ii Re-operative surgery in the neck and mediastinum should be considered, even when there are known distant metastases, to minimize the risk of large volume disease compromising the airway, oesophagus or laryngeal nerves **(4, D).**

Radiotherapy and chemotherapy. Palliative radiotherapy can play a valuable role in unresectable masses and painful bone metastases (Chapters 10.3 and 12.7).

Chemotherapy is now rarely used. Doxorubicin produces symptomatic response in <30% of cases; most are partial and of short duration. The same response rate is obtained when doxorubicin is used in combination with other drugs.

The selective uptake of ^{131}I-mIBG and ^{111}In-octreotide by 30–50% of medullary cancers generated interest in their potential therapeutic use.[50,51] Evidence supporting the role of high activity ^{131}I mIBG and ^{90}Y/^{177}Lu-labelled peptides in patients with inoperable, metastatic MTC is limited. A European survey reported durable symptom palliation in 61% of MTC patients treated with ^{131}I mIBG, with a reduction in biochemical markers in 39%,[52] but no randomised controlled trials have been undertaken.

There is phase II data for [^{90}yttrium- DOTA]-TOC showing response in patients with progressive disease and uptake on a diagnostic ^{111}In-octreotide scan.[53] Increased overall survival has been reported with pretargeted radioimmunotherapy using bi-specific monoclonal anti- CEA antibody and a ^{131}I-labeled bivalent hapten in patients with metastatic progressive MTC (defined with calcitonin doubling time <2 years), with a median overall survival of 110 vs. 61 months ($P < 0{\cdot}03$) in the experimental arm versus historical controls.[54]

i Routine use of radiolabelled molecules cannot be recommended but entry into trials should be considered. Treatment with unlabelled somatostatin analogues may help control severe diarrhoea from metastatic disease **(4, D).**[55,56]

Targeted therapies. Targeted therapies are the modality of choice for inoperable progressive and symptomatic disease. Vandetanib and cabozantanib (both tyrosine kinase inhibitors) have shown progression free survival advantage over placebo in prospective randomised controlled trials of 11 and 7 months respectively.[57,58] To date, neither drug has been shown to improve survival. The choice of initial drug will be based on the toxicity profiles and licensing indications. The presence or absence of a RET mutation did not significantly affect the response rates. Molecular profiling does not appear to aid with the choice of agent, but this is an evolving area of research.

For general information about targeted therapies see Chapter 12.7

i Treatment in this setting should preferably take place within a clinical trial **(4, D).**

Palliative care. Gastrointestinal symptoms often respond well to symptomatic treatment (such as loperamide and/or codeine phosphate).

i Medical therapy should concentrate on symptom control **(4, D).**

ii Somatostatin analogues are a possible alternative, which may decrease tumour peptide release **(4, D).**

iii Symptomatic distant metastases may respond to surgery, EBRT, thermoablation and chemoembolization (4, D).

iv Patients with known bony metastases may benefit from bisphosphonates or denosumab **(4, D).**

17.9. Molecular genetics

It is important to recognise the heritable forms of MTC because of the risk of other tumours in the individual and the family.[59–70] Early recognition and prophylactic surgery in MEN2/3 are effective in reducing both mortality and morbidity. Approximately 25% of MTCs are hereditary, as part of the MEN2/3 or FMTC syndromes. 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. Inherited MTC without other endocrinopathies also occurs. It is inherited in similar ways but tends to be more indolent than other forms of MTC.[71]

i 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 **(4, D).**

Genetic investigation of a patient with MTC. Clinical history—A clinical history that is suggestive of MEN2/3 syndromes would include:

- Symptoms/history of phaeochromocytoma, parathyroid disease;
- features of MEN3 (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).

i A systematic family history should be taken, to include all first- and second-degree relatives, with attention to features suggestive of MEN2/3 (thyroid, adrenal, parathyroid disease) The history must be recorded in the case notes.
Good Practice Point ☑

Genetic testing—Before testing.

i If expertise is not available within the primary clinical team, the patient should be offered genetic counseling and referred to the clinical genetics service **(4, D).**
Key recommendation
ii Because of the possibility of heritable disease, every case of MTC should be offered genetic testing **(4, D).**
iii Testing should always begin with the affected individual, if they are available **(4, D).**
iv If the affected individual is not available, the decision and strategy for testing should be discussed with the clinical genetics service **(4, D).**
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 **(4, D).**

Testing.

i Ideally 10 ml EDTA anticoagulated blood should be taken from the affected individual. Tests can be performed on smaller (e.g. 1–2 ml) amounts of blood (or buccal smears, or salivary samples), but this should be discussed with the appropriate NHS genetics laboratory **(4, D).**
ii The sample together with clinical details and family history should be sent to the appropriate NHS genetics laboratory **(4, D).**
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 13–16[65–68,72] **(2−, D).** Failure to screen exons 13–16 constitutes an incomplete test.
Key recommendation
iv Patients with clinical features of MEN3 (MEN2B) should be tested first for mutations in codons 918 and 922 (exon 16), 883 (exon 15) and 804 and 806 (exon 14) **(4, D).**
v Patients with clinical features of Hirschsprung's disease should be tested first for mutations in codons 609, 611, 618, 620 (exon 10) **(4, D).**

Action on results. If a mutation is found

i The result should be communicated, in the clinic, to the patient **(4, D).**
ii Permission must be obtained from the patient to disclose this result to anyone else, including the GP and family **(4, D).**
iii A plan should be made for the management of the individual and for the further investigation of the family **(4, D).**
iv *The individual.* Mutation implies MEN2/3 and thus (depending on the site of the mutation) a future risk of other MEN2/3 components such as further thyroid tumours, adrenal and parathyroid disease. *The family.* Family members at risk should be offered testing for the specific *RET* mutation **(4, D).**
v Contacting and investigating the family require expertise and co-ordination and should normally be undertaken by a specialist clinical genetics department, in liaison with the relevant clinical teams **(4, D).**

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 **(4, D).**
ii If there is strong presumptive evidence from the individual or family history of inherited disease: (a) discuss further with the clinical genetics department and consider research-based search for novel mutations **(4, D);** (b) consider biochemical screening of family members at risk using stimulated (intravenous calcium/pentagastrin, Appendix 1.2) 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 MEN 2 families (mostly with FMTC 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 CCH in the thyroid are suggestive of inherited disease, but not conclusive, nor does the absence of these features exclude it. The correct action in this situation is a matter for clinical judgment and may differ from family to family **(4, D).**

Mutation testing of tumour—If no blood sample is available from the affected individual, DNA may be obtainable from either frozen or paraffin-embedded tumour.

i 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 **(4, D).**
ii A somatic MEN3 (MEN2B)-type (codon 918) mutation is present in about 40% of sporadic tumours, but may also be present in tumours from MEN2A cases. This finding cannot therefore be used to exclude heritable disease.

17.10. Multiple Endocrine Neoplasia Type 3/2B (MEN3/2B)

Recognition. Photographs to aid diagnosis are provided in Appendix 2. MTC occurs early in MEN3 (MEN2B) and is particularly aggressive.[69,73]

i Any new patient with MTC, especially a child or young adult, should be carefully assessed for clinical features suggestive of MEN3[70,74–76] **(2−, C).**

ii More than 98% of MEN3 (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 MEN3 (MEN2B) with high probability. Where there is doubt, the patient should be referred for a specialist opinion,[70,77] **(4, D).**

Child of an MEN3 (MEN2B) patient.

i Because MEN3 (MEN2B) can present with clinically significant MTC in the neonatal period, management of the newborn child of a known carrier should be planned in advance with specialist advice **(4, D).**

ii Because MTC occurs early in MEN3 and is particularly aggressive, thyroid surgery in an affected child should be done as early as possible, preferably before the age of 12 months.[78] **(2−, C).**

iii Prenatal testing is possible. Couples who ask about prenatal testing for MEN3 (MEN2B) should be referred to a genetics clinic **(4, D).**

References

1 Modigliani, E., Cohen, R., Campos, J.M. *et al.* (1998) Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients. The GETC Study Group. Groupe d'étude des tumeurs à calcitonine. *Clinical Endocrinology*, **48**, 265–273.

2 2013/14 Standard Contract for Specialised Endocrinology Services (Adult). 2013.

3 Kloos, R.T., Eng, C., Evans, D.B. *et al.* (2009) Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid*, **19**, 565–612.

4 Pacini, F., Schlumberger, M., Dralle, H. *et al.* (2006) European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *European Journal of Endocrinology*, **154**, 787–803.

5 Costante, G., Durante, C., Francis, Z. *et al.* (2009) Determination of calcitonin levels in C-cell disease: clinical interest and potential pitfalls. *Nature Clinical Practice Endocrinology & Metabolism*, **5**, 35–44.

6 Chambon, G., Alovisetti, C., Idoux-Louche, C. *et al.* (2011) The use of preoperative routine measurement of basal serum thyrocalcitonin in candidates for thyroidectomy due to nodular thyroid disorders: results from 2733 consecutive patients. *Journal of Clinical Endocrinology and Metabolism*, **96**, 75–81.

7 Ahmed, S.R. & Ball, D.W. (2011) Clinical review: incidentally discovered medullary thyroid cancer: diagnostic strategies and treatment. *Journal of Clinical Endocrinology and Metabolism*, **96**, 1237–1245.

8 Machens, A., Hoffmann, F., Sekulla, C. *et al.* (2009) Importance of gender-specific calcitonin thresholds in screening for occult sporadic medullary thyroid cancer. *Endocrine-Related Cancer*, **16**, 1291–1298.

9 Lorenz, K., Elwerr, M., Machens, A. *et al.* (2013) Hypercalcitoninemia in thyroid conditions other than medullary thyroid carcinoma: a comparative analysis of calcium and pentagastrin stimulation of serum calcitonin. *Langenbeck's Archives of Surgery*, **398**, 403–409.

10 Machens, A. & Dralle, H. (2012) Biological relevance of medullary thyroid microcarcinoma. *Journal of Clinical Endocrinology and Metabolism*, **97**, 1547–1553.

11 Cohen, R., Campos, J.M., Salaun, C. *et al.* (2000) Preoperative calcitonin levels are predictive of tumor size and postoperative calcitonin normalization in medullary thyroid carcinoma. Groupe d'Etudes des Tumeurs a Calcitonine (GETC). *Journal of Clinical Endocrinology and Metabolism*, **85**, 919–922.

12 Machens, A., Schneyer, U., Holzhausen, H.J. *et al.* (2005) Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. *Journal of Clinical Endocrinology and Metabolism*, **90**, 2029–2034.

13 Machens, A., Lorenz, K. & Dralle, H. (2009) Individualization of lymph node dissection in RET (rearranged during transfection) carriers at risk for medullary thyroid cancer: value of pretherapeutic calcitonin levels. *Annals of Surgery*, **250**, 305–310.

14 Machens, A. & Dralle, H. (2010) Biomarker-based risk stratification for previously untreated medullary thyroid cancer. *Journal of Clinical Endocrinology and Metabolism*, **95**, 2655–2663.

15 Romei, C., Mariotti, S., Fugazzola, L. *et al.* (2010) Multiple endocrine neoplasia type 2 syndromes (MEN 2): results from the ItaMEN network analysis on the prevalence of different genotypes and phenotypes. *European Journal of Endocrinology*, **163**, 301–308.

16 Giraudet, A.L., Vanel, D., Leboulleux, S. *et al.* (2007) Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels. *Journal of Clinical Endocrinology and Metabolism*, **92**, 4185–4190.

17 Ganeshan, D., Paulson, E., Duran, C. *et al.* (2013) Current update on medullary thyroid carcinoma. *American Journal of Roentgenology*, **201**, 867–876.

18 Dromain, C., de Baere, T., Lumboso, J. *et al.* (2005) Detection of liver metastases from endocrine tumours: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. *Journal of Clinical Oncology*, **23**, 70–78.

19 Moley, J.F. (2010) Medullary thyroid carcinoma: management of lymph node metastases. *Journal of the National Comprehensive Cancer Network*, **8**, 549–556.

20 Pillarisetty, V.G., Katz, S.C., Ghossein, R.A. *et al.* (2009) Micromedullary thyroid cancer: how micro is truly micro? *Annals of Surgical Oncology*, **16**, 2875–2881.

21 Kazaure, H.S., Roman, S.A. & Sosa, J.A. (2012) Medullary thyroid microcarcinoma: a population-level analysis of 310 patients. *Cancer*, **118**, 620–627.

22 Machens, A., Gimm, O., Ukkat, J. *et al.* (2000) Improved prediction of calcitonin normalization in medullary thyroid carcinoma patients by quantitative lymph node analysis. *Cancer*, **88**, 1909–1915.

23 Machens, A., Hauptmann, S. & Dralle, H. (2008) Prediction of lateral lymph node metastases in medullary thyroid cancer. *British Journal of Surgery*, **95**, 586–591.

24 Machens, A., Holzhausen, H.J. & Dralle, H. (2004) Prediction of mediastinal lymph node metastasis in medullary thyroid carcinoma. *British Journal of Surgery*, **91**, 709–712.

25 Gimm, O., Ukkat, J. & Dralle, H. (1998) Determinative factors of biochemical cure after primary and reoperative surgery for sporadic medullary thyroid carcinoma. *World Journal of Surgery*, **22**, 562–567; discussion 567–568.

26 Skinner, M.A., Moley, J.A., Dilley, W.G. *et al.* (2005) Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. *New England Journal of Medicine*, **353**, 1105–1113.

27 Frank-Raue, K., Rybicki, L.A., Erlic, Z. *et al.* (2011) Risk profiles and penetrance estimations in multiple endocrine neoplasia type 2A caused by germline RET mutations located in exon 10. *Human Mutation*, **32**, 51–58.

28 Grubbs, E.G., Waguespack, S.G., Rich, T.A. *et al.* (2010) Do the recent American Thyroid Association (ATA) Guidelines accurately guide the timing of prophylactic thyroidectomy in MEN2A? *Surgery*, **148**, 1302–1309; discussion 1309–1310.

29 Machens, A., Niccoli-Sire, P., Hoegel, J. *et al.* (2003) Early malignant progression of hereditary medullary thyroid cancer. *New England Journal of Medicine*, **349**, 1517–1525.

30 Schreinemakers, J.M., Vriens, M.R., Valk, G.D. *et al.* (2010) Borel Rinkes IH. Factors predicting outcome of total thyroidectomy in young patients with multiple endocrine neoplasia type 2: a nationwide long-term follow-up study. *World Journal of Surgery*, **34**, 852–860.

31 Rohmer, V., Vidal-Trecan, G., Bourdelot, A. *et al.* (2011) Prognostic factors of disease-free survival after thyroidectomy in 170 young patients with a RET germline mutation: a multicenter study of the Groupe Francais d'Etude des Tumeurs Endocrines. *Journal of Clinical Endocrinology and Metabolism*, **96**, E509–E518.

32 Elisei, R., Romei, C., Renzini, G. *et al.* (2012) The timing of total thyroidectomy in RET gene mutation carriers could be personalized and safely planned on the basis of serum calcitonin: 18 years experience at one single center. *Journal of Clinical Endocrinology and Metabolism*, **97**, 426–435.

33 Leboulleux, S., Travagli, J.P., Caillou, B. *et al.* (2002) Medullary thyroid carcinoma as part of a multiple endocrine neoplasia type 2B syndrome: influence of the stage on the clinical course. *Cancer*, **94**, 44–50.

34 Brauckhoff, M., Machens, A., Lorenz, K. *et al.* (2014) Surgical curability of medullary thyroid cancer in multiple endocrine neoplasia 2B: a changing perspective. *Annals of Surgery*, **259**, 800–806.

35 Fife, K.M., Bower, M. & Harmer, C. (1996) Medullary thyroid cancer: the role of radiotherapy in local control. *European Journal of Surgical Oncology*, **22**, 588–591.

36 Hyer, S.L., Vini, L., A'Hern, R. *et al.* (2000) Medullary thyroid cancer: multivariate analysis of prognostic factors influencing survival. *European Journal of Surgical Oncology*, **26**, 686–690.

37 Wilson, P.C., Millar, B.M. & Brierley, J.D. (2004) The management of advanced thyroid cancer. *Clinical Oncology (Royal College of Radiologist)*, **16**, 561–568.

38 Royal College of Pathologists (2014) Dataset for Thyroid Cancer Histopathology Reports, 3rd edn. The Royal College of Pathologists, London.

39 The Royal College of Pathologists (2011) Dataset for Histopathology Reporting of Nodal Excisions and Neck Dissection Specimens Associated with Head and Neck Carcinomas, 3rd edn. The Royal College of Pathologists, London.

40 Brauckhoff, M., Gimm, O., Brauckhoff, K. *et al.* (2001) Calcitonin kinetics in the early postoperative period of medullary thyroid carcinoma. *Langenbeck's Archives of Surgery*, **386**, 434–439.

41 Ismailov, S.I. & Piulatova, N.R. (2004) Postoperative calcitonin study in medullary thyroid carcinoma. *Endocrine-Related Cancer*, **11**, 357–363.

42 Meijer, J.A., le Cessie, S., van den Hout, W.B. *et al.* (2010) Calcitonin and carcinoembryonic antigen doubling times as prognostic factors in medullary thyroid carcinoma: a structured meta-analysis. *Clinical Endocrinology*, **72**, 534–542.

43 http://www.thyroid.org/thyroid-physicians-professionals/calculators/thyroid-cancer-carcinoma/ (accessed 12 June 2014).

44 Yip, D.T., Hassan, M., Pazaitou-Panayiotou, K. *et al.* (2011) Preoperative basal calcitonin and tumor stage correlate with postoperative calcitonin normalization in patients undergoing initial surgical management of medullary thyroid carcinoma. *Surgery*, **150**, 1168–1177.

45 Treglia, G., Castaldi, P., Villani, M.F. *et al.* (2012) Comparison of ^{18}F-DOPA, ^{18}F-FDG and ^{68}Ga-somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma. *European Journal of Nuclear Medicine and Molecular Imaging*, **39**, 569–580.

46 Ong, S.C., Schroeder, H., Patel, S.G. *et al.* (2007) Diagnostic accuracy of 18F-FDG PET in restaging patients with medullary thyroid carcinoma and elevated calcitonin levels. *Journal of Nuclear Medicine*, **48**, 501–507.

47 Beheshti, M., Pocher, S., Vali, R. *et al.* (2009) The value of 18F-DOPA PET-CT in patients with medullary thyroid carcinoma: comparison with 18F-FDG PET-CT. *European Radiology*, **19**, 1425–1434.

48 Fialkowski, E., DeBenedetti, M. & Moley, J. (2008) Long-term outcome of reoperations for medullary thyroid carcinoma. *World Journal of Surgery*, **32**, 754–765.

49 Machens, A. & Dralle, H. (2013) Benefit-risk balance of reoperation for persistent medullary thyroid cancer. *Annals of Surgery*, **257**, 751–757.

50 Pasieka, J.L., McEwan, A.J. & Rorstad, O. (2004) The palliative role of 131I-MIBG and 111In-octreotide therapy in patients with metastatic progressive neuroendocrine neoplasms. *Surgery*, **136**, 1218–1226.

51 Kaltsas, G., Rockall, A., Papadogias, D. *et al.* (2004) Recent advances in radiological and radionuclide imaging and therapy of neuroendocrine tumours. *European Journal of Endocrinology*, **1511**, 15–27.

52 Hoefnagel, C.A. & Lewington, V.J. (2004) mIBG therapy. In: P.J. Ell, S.S. Gambhir eds. *Nuclear Medicine in Clinical Diagnosis and Treatment*, 3rd edn. Churchill Livingstone, Edinburgh, 445–457.

53 Iten, F., Müller, B., Schindler, C. *et al.* (2007) Response to [90Yttrium-DOTA]-TOC treatment is associated with long-term survival benefit in metastasized medullary thyroid cancer: a phase II clinical trial. *Clinical Cancer Research* **13**(Pt 1), 6696–6702.

54 Kraeber-Bodéré, F., Rousseau, C., Bodet-Milin, C. *et al.* (2006) Targeting, toxicity, and efficacy of 2-step, pretargeted radioimmunotherapy using a chimeric bispecific antibody and 131I-labeled bivalent hapten in a phase I optimization clinical trial. *Journal of Nuclear Medicine*, **47**, 247–255.

55 Vainas, I., Koussis, C., Pazaitou-Panayiotou, K. *et al.* (2004) Somatostatin receptor expression in vivo and response to somatostatin analog therapy with or without other antineoplastic treatments in advanced medullary thyroid carcinoma. *Journal of Experimental and Clinical Cancer Research*, **23**, 549–559.
56 Mahler, C., Verhelst, J., de Longueville, M. *et al.* (1990) Long-term treatment of metastatic medullary thyroid carcinoma with the somatostatin analogue octreotide. *Clinical Endocrinology*, **33**, 261–269.
57 Wells, S.A. Jr, Robinson, B.G., Gagel, R.F. *et al.* (2012) Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *Journal of Clinical Oncology*, **30**, 134–141.
58 Elisei, R., Schlumberger, M.J., Müller, S.P. *et al.* (2013) Cabozantinib in progressive medullary thyroid cancer. *Journal of Clinical Oncology*, **31**, 3639–3646.
59 Gagel, R.F., Cote, G.J., Martins Bugalho, M.J. *et al.* (1995) Clinical use of molecular information in the management of multiple endocrine neoplasia type A. *Journal of Internal Medicine*, **238**, 333–341.
60 Bolino, A., Schuffenecker, I., Luo, Y. *et al.* (1995) RET mutations in exons 13 and 14 of FMTC patients. *Oncogene*, **10**, 2415–2419.
61 Borrello, M.G., Smith, D.P., Pasini, B. *et al.* (1995) RET activation by germline MEN-2A and MEN-2B mutations. *Oncogene*, **11**, 2419–2427.
62 Eng, C., Clayton, D., Schuffenecker, I. *et al.* (1996) The relationship between specific ret protooncogene mutations and disease phenotype in multiple endocrine neoplasia type 2: International RET Mutation Consortium. *JAMA*, **276**, 1575–1579.
63 Eng, C., Mulligan, L.M., Smith, D.P. *et al.* (1995) Mutation of the RET protooncogene in sporadic medullary thyroid carcinoma. *Genes Chromosomes Cancer*, **12**, 209–212.
64 Lips, C.J., Landsvater, R.M., Hoppener, J.W. *et al.* (1994) Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. *New England Journal of Medicine*, **331**, 828–835.
65 Mulligan, L.M., Eng, C., Healey, C.S. *et al.* (1994) Specific mutations of the RET protooncogene are related to disease phenotype in MEN 2A and FMTC. *Nature Genetics*, **6**, 70–74.
66 Mulligan, L.M., Gardner, E., Smith, B.A. *et al.* (1993) Genetic events in tumour initiation and progression in multiple endocrine neoplasia type 2. *Genes Chromosomes Cancer*, **6**, 166–177.
67 Mulligan, L.M., Kwok, J.B., Healey, C.S. *et al.* (1993) Germline mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. *Nature*, **363**, 458–460.
68 Mulligan, L.M., Marsh, D.J., Robinson, B.G. *et al.* (1995) Genotype–phenotype correlation in MEN 2; report of the international RET mutations consortium. *Journal of Internal Medicine*, **238**, 343–346.
69 Wells, S.A., Dilley, W.G., Farndon, J.R. *et al.* (1985) Early diagnosis and treatment of medullary thyroid carcinoma. *Archives of Internal Medicine*, **145**, 1248–1252.
70 Samaan, N.A., Draznin, M.B., Halpin, R.E. *et al.* (1991) Multiple endocrine syndrome type IIB in early childhood. *Cancer*, **68**, 1832–1834.
71 Farndon, J.R., Leight, G.S., Dilley, W.G. *et al.* (1986) Familial medullary thyroid carcinoma without associated endocrinopathies: a distinct clinical entity. *British Journal of Surgery*, **73**, 278–281.
72 Mulligan, L.M., Eng, C., Attie, T. *et al.* (1994) Diverse phenotypes associated with exon 10 mutations of the RET protooncogene. *Human Molecular Genetics*, **3**, 2163–2167.
73 Russell, C.F., Van Heerden, J.A., Sizemore, G.W. *et al.* (1983) The surgical management of medullary thyroid carcinoma. *Annals of Surgery*, **197**, 42–48.
74 Laundau, D., Vini, L., Hern, R.A. *et al.* (2000) Thyroid cancer in children: the Royal Marsden Hospital experience. *European Journal of Cancer*, **36**, 214–220.
75 Marsh, D.J., McDowall, D., Hyland, V.J. *et al.* (1996) The identification of false positive responses to the pentagastrin stimulation test in RET mutation negative members of MEN 2A families. *Clinical Endocrinology*, **44**, 213–220.
76 O'Riordain, D.S., O'Brien, T., Crotty, T.B. *et al.* (1995) Multiple endocrine neoplasia type 2B: more than an endocrine disorder. *Surgery*, **118**, 936–942.
77 Carlson, K.M., Dou, S., Chi, D. *et al.* (1994) Single missense mutation in the tyrosine kinase catalytic domain of the RET protooncogene is associated with multiple endocrine neoplasia type 2B. *Proceedings of the National Academy of Sciences of the United States of America*, **91**, 1579–1583.
78 de Groot, J.W., Links, T.P., Plukker, J.T. *et al.* (2006) RET as a diagnostic and therapeutic target in sporadic and hereditary endocrine tumors. *Endocrine Reviews*, **27**, 535–560.

CHAPTER 18

18 Anaplastic thyroid cancer

Due to the rarity of this type of thyroid cancer coupled with its aggressive clinical course and short prognosis, it has proven difficult to conduct clinical trials and establish good quality evidence on which to base best practice. No single cancer centre will see a large number of patients and published series are usually single centre and extend over prolonged periods. Guidelines can only therefore make recommendations of weak strength based on low to moderate quality evidence.[1,2]

18.1. Background

Anaplastic thyroid cancer (ATC) is the rarest thyroid cancer subtype. There are estimated to be 70–90 new cases of ATC annually in the UK, accounting for 3–4% of all thyroid cancers.[3]

Decreasing incidence is reported by some and has been attributed to more accurate pathological diagnosis, more aggressive management of differentiated thyroid cancer (DTC) and an increase in dietary iodine.[4,5]

ATC occurs in an older population than seen in DTC, with most patients being over the age of 65. Fewer than 10% of patients are <50 years old at diagnosis. As with DTC there is a female preponderance (typically 60–70%). Risk factors for ATC are poorly understood although it can develop on a background of well DTC with reported rates of association ranging between 7% and 89%.[6–12]

The precipitating event in the de-differentiating pathway is uncertain and the mechanism of dedifferentiation is poorly understood. Multiple mutations have been reported in anaplastic thyroid cancer tumours including p53, RAS, BRAF, β-catenin, PIK3CA, Axin, APC, PTEN.[13,14]

Unfortunately, for the majority of patients regardless of the treatment approach, their cancer tends to grow rapidly, invade local tissues extensively and most patients die with uncontrolled local disease and distant metastases.

18.2. Presentation

There is a history of pre-existing goitre in a large proportion of patients, in up to many 80% of cases.[10,11]

Patients typically present with locally advanced neck disease. A 69% rate of tracheal invasion, 55% rate of oesophageal invasion and 39% rate of carotid artery involvement have been reported[15] and 15–50% may also have distant metastases.[16,17] Distant metastases most commonly involve lung and pleura (90%), bone (5–15%), and brain (5%).

Pathology. The commonest histological subtypes are spindle cell, pleomorphic giant cell and squamoid. A tumour may demonstrate one predominant pattern or a mixture of two or three different patterns.[6,18–20] Histological subtypes have no known prognostic significance, although there are reports of the rarer paucicellular variant, affecting younger patients and demonstrating a more indolent course.[8,21,22] The differential diagnosis may include poorly DTC, squamous cell carcinoma, lymphoma, sarcoma and metastatic lesions.

i The histopathology should be reviewed by the thyroid MDT histopathologist in all cases, in order to ensure less aggressive and more treatable thyroid cancer subtypes are not misdiagnosed.
Good Practice Point ☑

The pathology report following thyroidectomy should provide information on the proportion of tumour that comprises anaplastic thyroid cancer and any coexisting differentiated or poorly DTC in accordance with the Royal College of Pathologists standards and datasets for thyroid cancer histopathology reports (see Chapter 16) as this may affect prognosis and help guide patient management **(4, D).**

18.3. Investigation

Physical examination to assess the clinical evidence of extent of local and distant disease and an assessment of the patient's performance status is important. Due to the locally infiltrative nature of the disease and the likelihood of extensive extrathyroidal tumour extension, surgery is only expected to be suitable in a small minority of patients.

i Fine needle aspiration cytology (FNAC) and/or core biopsy may be required to establish a diagnosis. There is a wide variation in histological appearance and many tumours exhibit a mixed morphology. Necrosis and inflammatory changes are common and FNAC samples may fail to capture representative tissue to allow diagnosis. In these cases consideration should be given to core biopsy or open biopsy rather than a repeat FNAC attempt **(4,D).**

ii Imaging investigations with ultasound (US), computed tomography (CT) or magnetic resonance imaging (MRI) of the neck should be performed to assess the extent of local disease, in particular invasion of the great vessels and upper aero-digestive tract, and to determine whether surgical resection is feasible.
Good Practice Point ☑

iii Assessment for distant metastases with CT of chest and abdomen is recommended, as a significant number of patients will have extensive disease. CT imaging of pelvis and brain may also need to be considered depending on patients'

symptoms and whether a radical treatment approach is feasible **(4,D).**

iv If disease appears localised and amenable to surgery, the patient should undergo nasendoscopy examination to assess vocal cord function and to assess for evidence of direct involvement of larynx and upper trachea **(4,D).**

18.4. Staging

All ATCs are considered as TNM stage IV (Table 18.1). Stage IVa refers to intrathyroidal disease, stage IVb to gross extra-thyroidal extension and stage IVc to patients with distant metastatic disease. A small proportion (2–6%) may be diagnosed as an incidental finding in a thyroidectomy specimen.[23–25]

It is expected that 10% of patients will present with stage IVa disease, 40% with stage IVb and 50% with stage IVc disease.[26,27]

18.5. Prognosis

The best results for local control and survival in numerous studies result from multimodality treatment with surgical resection followed by radical external beam radiotherapy (EBRT) and chemotherapy.[28–30] Selection bias is however a significant factor as only patients with localised disease, good performance status and a generally younger patient cohort have been treated with this option. The majority of patients presenting with ATC will have advanced disease not amenable to resection and a radical treatment approach. Median survival is in the range of 3–7 months[31] and 1-year survival 10–20%.[14,32] Prognostic factors associated with a poorer outcome include advanced stage, older age, male sex, large tumour size, presentation with acute symptoms, distant metastases, leukocytosis.[33,34] Better prognosis has been observed when ATC coexists with DTC.[35]

18.6. Treatment

In view of the rapidly progressive behaviour of this disease, prompt investigation and discussion at the thyroid multidisciplinary meeting (MDM) is needed in order to establish a management plan. This is particularly important if the patient appears to have localised disease and may be amenable to radical treatment options. Multimodality treatment with R0/R1 thyroidectomy and chemoradiotherapy has shown the most favourable outcomes although only for a minority of patients who undergo this intense and toxic treatment.[36–39] The optimal sequence of treatment, chemotherapy agents and doses along with EBRT fractionation and technique are yet to be defined.

Table 18.1. Staging for ATC

Stage	TNM classification			5-year relative survival*
All stages				7%
IVA	T4a	Any N	M0	
IVB	T4b	Any N	M0	
IVC	Any T	Any N	M1	

*http://www.cancer.org/cancer/thyroidcancer/detailedguide/thyroid-cancer-survival-rates.

i New diagnoses of ATC should be discussed promptly at the MDM **(4, D).**

ii Initial assessment should focus in identifying the small proportion of patients with localised disease and good performance status, that may benefit from surgical resection and other adjuvant therapies **(4, D).**

Key recommendation

iii Realistic discussion with the patient of treatment aims, benefits and outcomes before undertaking any interventions, is recommended **(4, D).**

iv Patients and their carers should have access to good quality information (Appendix 4, Patient Information Leaflet 7).

Good Practice Point ☑

Surgery. When deciding on suitability for resection, the extent of local infiltration is important in deciding whether a R0 or R1 resection can be achieved without significant morbidity and mortality. Approximately a third of thyroidectomy operations will require an extended resection.[4] Provided complete tumour resection can be achieved, survival may be prolonged.[7,31,40,41] Neoadjuvant non-surgical therapy has been shown to convert unresectable to resectable disease in selected patients.[32] Surgery with mere intent of debulking, rather than complete tumour resection is unlikely to achieve beneficial local control or improved survival. There is no role for thyroidectomy in the presence of distant metastatic disease.

i Tumours that are small and intra-thyroidal or involve easily excised structures should be treated by total thyroidectomy, therapeutic lymph node dissection and where extra-thyroidal invasion is present, en bloc resection.

Good Practice Point ☑

ii The surgical intent should be gross tumour resection and not merely an attempt at debulking.

Good Practice Point ☑

Key recommendation

iii Consideration of elective tracheostomy may be necessary in cases of advanced local disease. Although this procedure may avoid asphyxia and avert impending death, it may also prolong suffering and is often not in the patient's best interests **(4, D).** In such cases **Personalised Decision Making** is recommended (Chapter 2.4) **(4, D).**

iv If a patient is being considered for radical surgery, EBRT or chemoradiotherapy and has swallowing difficulties, consideration should be given to gastrostomy placement **(4, D).**

EBRT. The evidence base is limited as no prospective randomised controlled trials (RCTs) have been undertaken but reduced morbidity and mortality from loco-regional disease has been reported. Clear guidance on dose and fractionation regimes cannot be given but doses >40 Gy have resulted in the best outcomes.[23,42,43] Hyperfractionation (1·2 Gy bd) with or

without acceleration in combination with chemotherapy has been advocated by some investigators but despite an intense regimen with significant toxicity only 9% of patients survived 2 years.[44,45] Another study of hyperfractionation and acceleration reported clinical response rate (partial and complete responses) of 59% and stable disease in a further 29%, but toxicity was deemed unacceptable and all patients died within 8 months.[46] The addition of concurrent chemotherapy may improve the 1-year survival rate, but dual modality treatment increases toxicity and may not improve survival. Concurrent chemotherapy regimens that have been used include: cisplatin weekly, doxorubicin weekly or 3 weekly, paclitaxel/carboplatin weekly, docetaxel/doxorubicin 3–4 weekly and paclitaxel weekly.[7,40]

i There is lack of consensus on optimal management of small intrathyroidal anaplastic thyroid cancers or incidentally found anaplastic thyroid cancers following surgery. Some advocate adjuvant therapy whilst others favour regular clinical review and frequent cross sectional imaging. In such cases **Personalised Decision Making** is recommended (Chapter 2.4) **(4, D).**

ii Following an R0 or R1 thyroid resection in patients of good performance status (WHO PS 0–1) and with no evidence of distant metastases, consideration should be given to adjuvant radical EBRT ± concurrent chemotherapy **(4, D).**

iii When indicated, EBRT should commence as soon as the patient has recovered from surgery.

Good Practice Point ☑

iv If thyroidectomy is not appropriate but disease is localised, consideration should be given to radical EBRT, with or without concurrent chemotherapy aiming for local disease control **(4, D).** Such patients should be restaged after EBRT and surgical resection reconsidered **(4, D).**

v Intensity modulated radiotherapy (IMRT) allows the delivery of a more conformal and hence higher dose with improved dose homogeneity across both gross disease and high risk areas. IMRT should be utilised where available for radical treatment plans.

Good Practice Point ☑

vi Palliative EBRT to the thyroid mass may provide symptomatic benefit for selected patients with pain and obstructive symptoms, but local disease and symptom progression despite EBRT is common and must be discussed with the patient **(4, D).**

vii EBRT may also be considered for palliation of symptomatic distant metastases. Hypofractionated regimens are most practicable in the setting of advanced disease (See Chapter 10) **(4,D).**

Systemic therapy for advanced disease. Localised symptoms are usually better palliated with focal therapy (e.g. EBRT). Systemic therapy is worthy of consideration in advanced disease. However, there is no conclusive evidence that survival or quality of life is improved with systemic oncological therapy, though some patients may achieve valuable symptomatic palliation.

Chemotherapy: commonly used regimes include single agent doxorubicin or epirubicin, doxorubicin and cisplatin, paclitaxel[47,48] and paclitaxel and carboplatin.[47–49]

Targeted therapy: Phase 2 trials of axitinib[50] (an inhibitor of VEGFR 1–3, PDGFR, cKIT) and sorafenib[51,52] (an inhibitor of VEGFR, PDGFR and RAF kinases) have been disappointing.

A randomised phase 2 study of fosbretabulin (a vascular disrupting agent that selectively targets tumour neovasculature), after thyroidectomy in combination with paclitaxel and carboplatin,[53] reported improved 1-year survival in a selected subgroup of patients (25·5% *vs* 8·7%). The study closed before target recruitment was achieved, therefore statistically significant conclusions cannot be made.

Information on ongoing available clinical trials can be found in relevant websites.[54]

Systemic anti-cancer treatment may not be deemed clinically appropriate in all cases nor desired by all patients. Best supportive care and symptom control is a vital part of patient management.

i For patients who wish to receive aggressive treatment and who are of good performance status (WHO PS 0–2) with locally advanced or metastatic disease, consideration should be given to systemic therapy. It is important to discuss the potential risks and uncertain benefits with the patient and to have realistic goals **(4, D).**

ii Given the poor outcome with current standard therapies, patients should be considered for clinical trials where appropriate and available **(4, D).**

iii Tumour molecular profiling should be encouraged in order to help design interventional studies **(4, D).**

iv Consideration should be given to donating anaplastic thyroid cancer tissue to tissue banks in order to facilitate the discovery of potential therapeutic targets and drug design **(4, D).**

v Patients should be offered referral to local palliative care teams and support services **(4, D).**

References

1 Smallridge, R.C., Ain, K.B., Asa, S.L. *et al.* (2012) American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid*, **22**, 1104–1139.

2 NCCN (2012) 2012 Guidelines version 3. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site

3 OCIU (2012) UK data estimated from England anaplastic thyroid cancer data provided by Oxford Cancer Intelligence Unit.

4 Passler, C., Scheuba, C., Prager, G. *et al.* (1999) Anaplastic (undifferentiated) thyroid carcinoma (ATC). A retrospective analysis. *Langenbeck's Archives of Surgery*, **384**, 284–293.

5 Dijkstra, B., Prichard, R.S., Lee, A. *et al.* (2007) Changing patterns of thyroid carcinoma. *Irish Journal of Medical Science*, **176**, 87–90.

6 Carcangiu, M.L., Steeper, T., Zampi, G. *et al.* (1985) Anaplastic thyroid carcinoma. A study of 70 cases. *American Journal of Clinical Pathology*, **83**, 135–158.

7 Venkatesh, Y.S., Ordonez, N.G., Schultz, P.N. *et al.* (1990) Anaplastic carcinoma of the thyroid. A clinicopathologic study of 121 cases. *Cancer*, **66**, 321–330.

8 Nishiyama, R.H., Dunn, E.L. & Thompson, N.W. (1972) Anaplastic spindle-cell and giant-cell tumors of the thyroid gland. *Cancer*, **30**, 113–127.

9 Van der Laan, B.F., Freeman, J.L., Tsang, R.W. *et al.* (1993) The association of well-differentiated thyroid carcinoma with insular or anaplastic thyroid carcinoma; evidence for dedifferentiation in tumor progression. *Endocrine Pathology*, **4**, 215–221.

10 Aldinger, K.A., Samaan, N.A., Ibanez, M. *et al.* (1978) Anaplastic carcinoma of the thyroid: a review of 84 cases of spindle and giant cell carcinoma of the thyroid. *Cancer*, **41**, 2267–2275.

11 LiVolsi, V.A. (1990) Surgical Pathology of the Thyroid. W.B. Saunders, Philadelphia, PA.

12 Spires, J.R., Schwartz, M.R. & Miller, R.H. (1988) Anaplastic thyroid carcinoma. Association with differentiated thyroid cancer. *Archives of Otolaryngology – Head and Neck Surgery*, **114**, 40–44.

13 Smallridge, R.C., Marlow, L.A. & Copland, J.A. (2009) Anaplastic thyroid cancer: molecular pathogenesis and emerging therapies. *Endocrine-Related Cancer*, **16**, 17–44.

14 Smallridge, R.C. & Copland, J.A. (2010) Anaplastic thyroid carcinoma: pathogenesis and emerging therapies. *Clinical Oncology (Royal College of Radiologists (Great Britain))*, **22**, 486–497.

15 Zhang, Z.M., Xu, Z.G., Tang, P.Z. *et al.* (2006) [A retrospective analysis of anaplastic thyroid carcinoma]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*, **28**, 322–324.

16 Thompson, L.D., Wieneke, J.A., Paal, E. *et al.* (2001) A clinicopathologic study of minimally invasive follicular carcinoma of the thyroid gland with a review of the English literature. *Cancer*, **91**, 505–524.

17 O'Neill, J.P. & Shaha, A.R. (2013) Anaplastic thyroid carcinoma. *Oral Oncology*, **49**, 702–706.

18 Rosai, J., Carcangiu, M.L. & DeLellis, R.A. (1992) Undifferentiated (anaplastic) carcinoma. In: J. Rosai, M.L. Carcangiu, R.A. DeLellis eds. Tumors of the Thyroid Gland, 3rd edn. Armed Forces Institute of Pathology, Washington, DC, 135–159.

19 Albores-Saavedra, J., Henson, D.E., Glazer, E. *et al.* (2007) Changing patterns in the incidence and survival of thyroid cancer with follicular phenotype – papillary, follicular, and anaplastic: a morphological and epidemiological study. *Endocrine Pathology*, **18**, 1–7.

20 Seethala, R.R. & Nikiforov, Y.E. (2009) Anaplastic (undifferentiated) carcinoma. In: Y.E. Nikiforov, P.W. Biddinger, L.D.R. Thompson eds. Diagnostic Pathology and Molecular Genetics of the Thyroid: A Comprehensive Guide for Practicing Thyroid Pathology. Lippincott Williams & Wilkins, Philadelphia, PA, 228–248.

21 Wan, S.K., Chan, J.K. & Tang, S.K. (1996) Paucicellular variant of anaplastic thyroid carcinoma. A mimic of Reidel's thyroiditis. *American Journal of Clinical Pathology*, **105**, 388–393.

22 Canos, J.C., Serrano, A. & Matias-Guiu, X. (2001) Paucicellular variant of anaplastic thyroid carcinoma: report of two cases. *Endocrine Pathology*, **12**, 157–161.

23 Pierie, J.P., Muzikansky, A., Gaz, R.D. *et al.* (2002) The effect of surgery and radiotherapy on outcome of anaplastic thyroid carcinoma. *Annals of Surgical Oncology*, **9**, 57–64.

24 Besic, N., Hocevar, M., Zgajnar, J. *et al.* (2005) Prognostic factors in anaplastic carcinoma of the thyroid – a multivariate survival analysis of 188 patients. *Langenbeck's Archives of Surgery*, **390**, 203–208.

25 Voutilainen, P.E., Multanen, M., Haapiainen, R.K. *et al.* (1999) Anaplastic thyroid carcinoma survival. *World Journal of Surgery*, **23**, 975–978.

26 McIver, B., Hay, I.D., Giuffrida, D.F. *et al.* (2001) Anaplastic thyroid carcinoma: a 50-year experience at a single institution. *Surgery*, **130**, 1028–1034.

27 Chen, J., Tward, J.D., Shrieve, D.C. *et al.* (2008) Surgery and radiotherapy improves survival in patients with anaplastic thyroid carcinoma: analysis of the surveillance, epidemiology, and end results 1983–2002. *American Journal of Clinical Oncology*, **31**, 460–464.

28 Ito, K., Hanamura, T., Murayama, K. *et al.* (2012) Multimodality therapeutic outcomes in anaplastic thyroid carcinoma: improved survival in subgroups of patients with localized primary tumors. *Head and Neck*, **34**, 230–237.

29 Haigh, P.I., Ituarte, P.H., Wu, H.S. *et al.* (2001) Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. *Cancer*, **91**, 2335–2342.

30 Swaak-Kragten, A.T., de Wilt, J.H., Schmitz, P.I. *et al.* (2009) Multimodality treatment for anaplastic thyroid carcinoma–treatment outcome in 75 patients. *Radiotherapy and Oncology*, **92**, 100–104.

31 Untch, B.R. & Olson, J.A. (2006) Anaplastic thyroid carcinoma, thyroid lymphoma and metastasis to thyroid. *Surgical Oncology Clinics of North America*, **15**, 661–679.

32 Kebebew, E. (2012) Anaplastic thyroid carcinoma; rare, fatal and neglected. *Surgery*, **152**, 1088–1089.

33 Fujita, T., Ogasawara, Y., Naito, M. *et al.* (2006) Anaplastic thyroid carcinoma associated with granulocyte colony-stimulating factor: report of a case. *Surgery Today*, **36**, 63–67.

34 Sato, T., Omura, M., Saito, J. *et al.* (2000) Neutrophilia associated with anaplastic carcinoma of the thyroid: production of macrophage colony-stimulating factor (M-CSF) and interleukin-6. *Thyroid*, **10**, 1113–1118.

35 Kitamura, Y., Shimizu, K., Nagahama, M. *et al.* (1999) Immediate causes of death in thyroid carcinoma: clinicopathological analysis of 161 fatal cases. *Journal of Clinical Endocrinology and Metabolism*, **84**, 4043–4049.

36 Smallridge, R.C. (2012) Approach to the patient with anaplastic thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism*, **97**, 2566–2572.

37 Brignardello, E., Gallo, M., Baldi, I. *et al.* (2007) Anaplastic thyroid carcinoma: clinical outcome of 30 consecutive patients referred to a single institution in the past 5 years. *European Journal of Endocrinology*, **156**, 425–430.

38 Foote, R.L., Molina, J.R., Kasperbauer, J.L. *et al.* (2011) Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single-institution experience using aggressive multimodal therapy. *Thyroid*, **21**, 25–30.

39 Derbel, O., Limem, S., Ségura-Ferlay, C. *et al.* (2011) Results of combined treatment of anaplastic thyroid carcinoma (ATC). *BMC Cancer*, **11**, 469.

40 Junor, E.J., Paul, J. & Reed, N.S. (1992) Anaplastic thyroid carcinoma: 91 patients treated by surgery and radiotherapy. *European Journal of Surgical Oncology*, **18**, 83–88.

41 Bisof, V., Rakusic, Z. & Despot, M. (2014) Treatment of patients with anaplastic thyroid cancer during the last 20 years: whether any progress has been made? *European Archives of Otorhinolaryngology*, [Epub ahead of print].

42 Wang, Y., Tsang, R., Asa, S. *et al.* (2006) Clinical outcome of anaplastic thyroid carcinoma treated with radiotherapy of once- and twice-daily fractionation regimens. *Cancer*, **107**, 1786–1792.

43 Tan, R.K., Finley, R.K. 3rd, Driscoll, D. *et al.* (1995) Anaplastic carcinoma of the thyroid: a 24-year experience. *Head and Neck*, **17**, 41–44.
44 Tennvall, J., Lundell, G., Wahlberg, P. *et al.* (2002) Anaplastic thyroid carcinoma: three protocols combining doxorubicin, hyperfractionated radiotherapy and surgery. *British Journal of Cancer*, **86**, 1848–1853.
45 De Crevoisier, R., Baudin, E., Bachelot, A. *et al.* (2004) Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy and hyperfractionated accelerated external radiotherapy. *International Journal of Radiation Oncology Biology Physics*, **60**, 1137–1143.
46 Mitchell, G., Huddart, R. & Harmer, C. (1999) Phase II evaluation of high dose accelerated radiotherapy for anaplastic thyroid carcinoma. *Radiotherapy and Oncology*, **50**, 33–38.
47 Ain, K.B. & Egorin, M.J. (2000) DeSimone PA 2000 Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six hour infusion. Collaborative anaplastic thyroid cancer health intervention trials (CATCHIT) group. *Thyroid*, **10**, 587–594.
48 Higashiyama, T., Ito, Y., Hirokawa, M. *et al.* (2010) Induction chemotherapy with weekly paclitaxel administration for anaplastic thyroid carcinoma. *Thyroid*, **20**, 7–14.
49 Bhatia, A., Rao, A., Ang, K.K. *et al.* (2010) Anaplastic thyroid cancer: clinical outcomes with conformal radiotherapy. *Head and Neck*, **32**, 829–836.
50 Cohen, E.E., Rosen, L.S., Vokes, E.E. *et al.* (2008) Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. *Journal of Clinical Oncology*, **26**, 4708–4713.
51 Kloos, R.T., Ringel, M.D., Knopp, M.V. *et al.* (2009) Phase II trial of sorafenib in metastatic thyroid cancer. *Journal of Clinical Oncology*, **27**, 1675–1684.
52 Nagaiah, G., Fu, P., Wasman, J.K. *et al.* (2009) Phase II trial of sorafenib (bay 43-9006) in patients with advanced anaplastic carcinoma of the thyroid (ATC). *Journal of Clinical Oncology*, **27** (suppl 15), A6058.
53 Sosa, J.A., Balkissoon, J., Lu, S.P. *et al.* (2012) Thyroidectomy followed by fosbretabulin (CA4P) combination regimen appears to suggest improvement in patient survival in anaplastic thyroid cancer. *Surgery*, **152**, 1078–1087.
54 http://public.ukcrn.org.uk/search/Portfolio.aspx?Level1=1&Level2=7 http://www.clinicaltrials.gov

CHAPTER 19

19 Long-term survivorship

Most patients with thyroid cancer who have been treated optimally have similar life expectancies as the background population. Yet quality of life has been shown in some studies to be impaired.[1,2] Why that should be the case is unclear, but possible contributors include: instability of thyroid status and calcium homeostasis, uncertainty and worry about health and the future, emotional, psychological, social and financial consequences of the diagnosis of cancer and its treatment.

The clinical team should endeavor to provide support and prevent or minimise iatrogenic complications that add to patients' burden. The MacMillan service, patient-led organisations (Appendix 4) and clinical psychologists play an important role in providing information and support and should be engaged when appropriate.

Avoidance of iatrogenic complications

i Dysthyroidism should be avoided whenever possible.
Good Practice Point ☑

ii The treatment of hypoparathyroidism should be supervised by experienced clinicians and monitored appropriately so as to avoid hyper- and hypocalcaemia (Chapter 11.2).
Good Practice Point ☑

iii Appropriate measures should be taken to avoid osteoporosis and cardiac complications of suppressive thyroxine therapy in patients at risk (Chapter 11.5).
Good Practice Point ☑

Communication with patients

Uncertainty fuels anxiety and may impact significantly on quality of life. Good quality information and patient engagement in decision-making (Chapter 2.4) are generally valued by most patients. Risk stratification after surgery (Chapter 2.3) provides a reasonable basis for estimating the likelihood of tumour recurrence. Within the first 12 months of initial treatment, most patients will have had restaging [by measurement of stimulated thyroglobulin (Tg), ultrasound (US) of neck and in some cases additional investigations]. Dynamic Risk Stratification (Chapter 2.3) can identify patients with an extremely low risk of future recurrence, irrespective of the original stage.[3] Other studies have shown that a stimulated serum Tg (sTg) <0.5 μg/l in the absence of anti-Tg antibody has an approximately 98–99.5% chance of identifying patients completely free of thyroid cancer on follow-up.[4,5]

i The clinical team should offer the opportunity to patients to discuss their prognosis at the time of their presentation and offer good quality written material relevant to their disease (Appendix 4).
Good Practice Point ☑

ii Shared-decision making should be offered.
Good Practice Point ☑

iii The clinical team should offer the opportunity to patients to discuss their prognosis after restaging.
Good Practice Point ☑

iv The clinical team should ensure that those patients who after restaging are shown to have a risk of recurrence <1–2% are aware of their good prognosis.
Good Practice Point ☑

v Patients should be informed about the purpose of investigations and the significance of information that may be forthcoming as a result of the investigations.
Good Practice Point ☑

vi Patients should be informed about the outcome of investigations promptly and be offered to opportunity to discuss the significance of the results.
Good Practice Point ☑

vii Patients with a low risk of recurrence should be informed about the need for continued monitoring of their thyroid status when they are referred back to their GP.
Good Practice Point ☑

References

1 Husson, O., Haak, H.R., Buffart, L.M. *et al.* (2013) Health-related quality of life and disease specific symptoms in long-term thyroid cancer survivors: a study from the population-based PROFILES registry. *Acta Oncologica*, **52**, 249–258.

2 Singer, S., Lincke, T., Gamper, E. *et al.* (2012) Quality of life in patients with thyroid cancer compared with the general population. *Thyroid*, **22**, 117–124.

3 Tuttle, R.M., Tala, H., Shah, J. *et al.* (2010) Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. *Thyroid*, **20**, 1341–1349.

4 Kloos, R.T. & Mazzaferri, E.L. (2005) A single recombinant human thyrotrophin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. *Journal of Clinical Endocrinology and Metabolism*, **90**, 5047–5057.

5 Castagna, M.G., Brilli, L., Pilli, T. *et al.* (2008) Limited value of repeat recombinant thyrotropin (rhTSH)- stimulated thyroglobulin testing in differentiated thyroid carcinoma patients with previous negative rhTSH- stimulated thyroglobulin and undetectable basal serum thyroglobulin levels. *Journal of Clinical Endocrinology and Metabolism*, **93**, 76–81.

CHAPTER 20

20 Registration, core dataset and audit

It is mandatory for all patients with thyroid cancer in England and Wales to be registered within a regional cancer network. Further information on the core dataset can be found on: www.ncin.org.uk. The Cancer Outcomes and Services Dataset (COSD) is the national standard for reporting cancer in the NHS in England. It replaced the National Cancer Dataset and the Cancer Registration Dataset and includes additional site-specific data items relevant to the different tumour types.[1] The Welsh Cancer Intelligence and Surveillance Unit is the National Cancer Registry for Wales,[2] ISD (Information Services Division) Scotland is Scottish Cancer Registry[3] and the Northern Ireland Cancer Registry is the corresponding agency in Northern Ireland.[4]

i The RCPath has produced a 3rd edition of the Dataset for thyroid cancer histopathology reports in 2014[5] to assist pathologists in providing a high standard of care for patients and its use is recommended **(4, D).**

ii The British Association of Endocrine and Thyroid Surgeons is engaged in regular national audits,[6] which are informative and participation of all surgeons undertaking thyroid surgery for cancer in these audits is recommended **(4, D).**

iii Prospective data collection and regular national audit of outcomes and processes should be carried out. **National Cancer Peer Review Programme, measure 11-1C-111i**[7]

References

1 http://www.ncin.org.uk/collecting_and_using_data/data_collection/cancer_outcomes_and_services_dataset_cosd_latest_downloads
2 http://www.wales.nhs.uk/sites3/home.cfm?orgid=242
3 http://www.isdscotland.org/Health-Topics/Cancer/
4 http://www.publichealth.hscni.net/directorate-public-health/service-development-and-screening/northern-ireland-cancer-registry
5 http://www.rcpath.org/publications-media/publications/datasets/thyroid-cancer.htm
6 http://www.baets.org.uk/audit/
7 http://www.mycancertreatment.nhs.uk/wpcontent/themes/mct/uploads/2012/09/resources_measures_HeadNeck_Measures_April2011.pdf.

CHAPTER 21

21 Thyroid cancer: a guide for general practitioners

21.1. Raising awareness

Thyroid nodules, particularly when solitary and clinically obvious, should be investigated as they carry a small but significant malignant potential (about 10% or less).

Cancer of the thyroid is rare, representing only about 1% of all cancers. The overall 10-year survival rate for differentiated thyroid cancer (DTC) is 80–90%. Five to twenty percent of patients develop local or regional recurrences and 10–15% develop distant metastases.

21.2. Prevention

Previous head or neck irradiation in childhood is a cause of thyroid cancer in adults. Exposure to radiation should be limited whenever possible. Nuclear fallout is a well recognised cause of increased risk of thyroid cancer. If populations or individuals are contaminated with radioactive iodine, the thyroid can be protected by administering potassium iodide.[1,2]

21.3. Screening

No screening is indicated for the general population. Risk-directed screening should be considered (by referral to the specialist secondary team) when the GP identifies patients with:

- familial thyroid cancer, including medullary thyroid cancer (MTC)
- history of neck irradiation in childhood
- family history of multiple endocrine neoplasia type 2A (MEN2A) or type 3 (MEN3, previously MEN2B)

Patients with 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

21.4. 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)

MTC is rare, but any features that raise the possibility of MTC [family history of MTC, thyroid lump associated with diarrhoea, thyroid lump with a history suggestive of phaeochromocytoma, phenotype suggestive of MEN3 (Appendix 2)] should lead to an urgent referral.

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 special interest in thyroid cancer and is a member of the regional thyroid cancer multidisciplinary team (MDT).

Non-urgent referrals. The following patients should be referred in the normal way:

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

Physical examination. Examination should focus 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.

Pulse and blood pressure should be noted.

Appropriate investigations pending hospital appointment. Thyroid function tests should be requested by the GP and appended to the referral letter. Hyperthyroidism or hypothyroidism

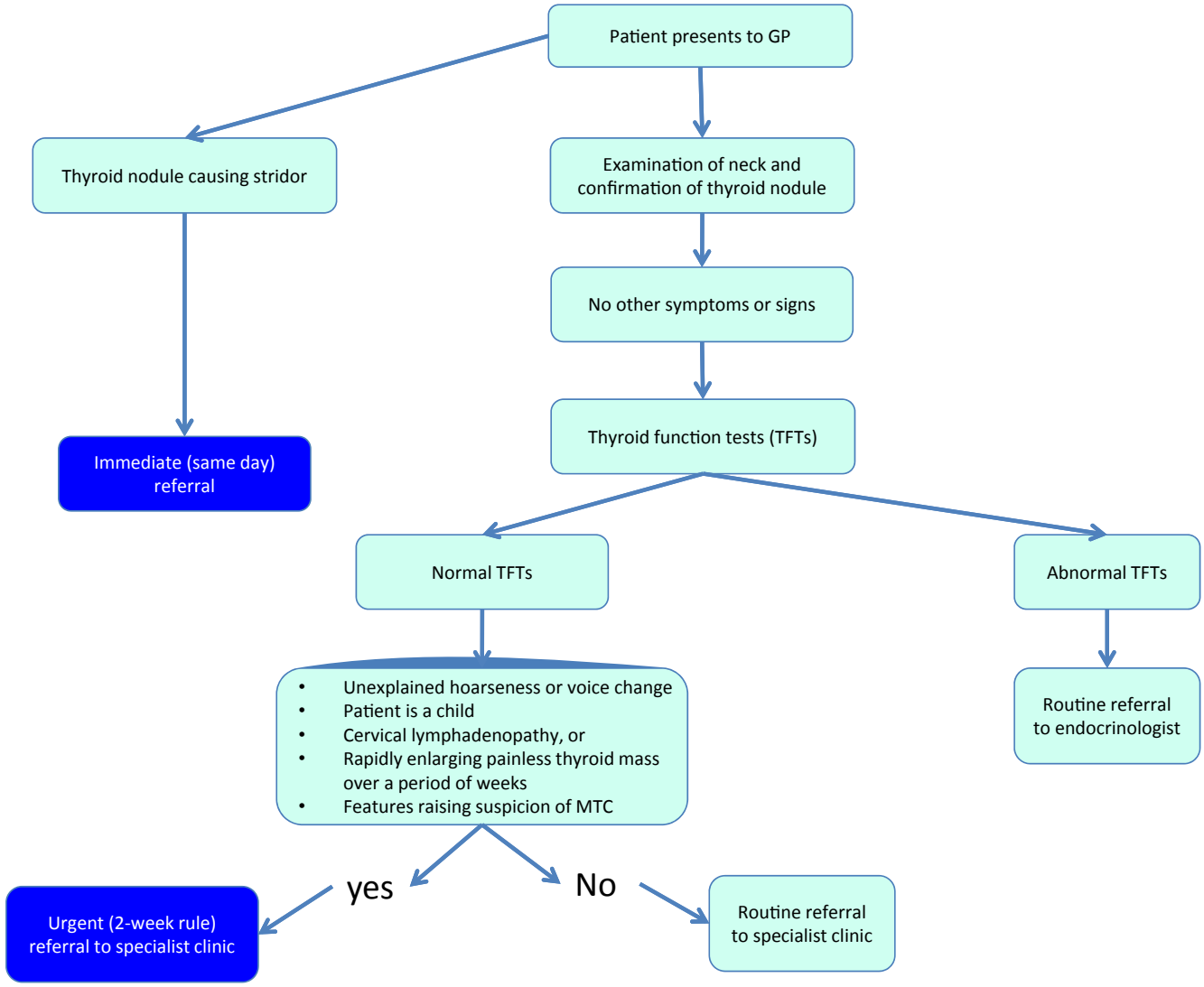


Fig. 21.1 Algorithm for the diagnosis and management of a thyroid nodule or suspected thyroid cancer in general practice.

associated with a nodular goitre is unlikely to be thyroid cancer; these patients should be referred routinely to an endocrinologist.

Initiation of other investigations [such as ultrasound (US) scanning or autoantibodies] by the GP is unnecessary and may cause delay in making the diagnosis of cancer.

The diagnosis and management of a thyroid nodule or suspected thyroid cancer in general practice is presented in schematic form in Fig. 21.1.

Communicating the diagnosis. Informing the primary care team

i The GP should be informed of the diagnosis of thyroid cancer being communicated to the patient for the first time by the end of the following working day.
National Cancer Peer Review Programme, measure11-2I-111
Key recommendation

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 counseling 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.

21.5. 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.

Patients will commonly undergo thyroidectomy, followed in some cases by an ablative dose of radioiodine (^{131}I).

Thereafter patients will generally require levothyroxine to suppress TSH to <0.1 mU/l and some will need treatment to correct hypocalcaemia.

Measurement of serum thyroglobulin (Tg) will be performed at regular intervals to detect possible recurrence.

Patients will be provided with written and verbal information about the disease and its management (Patient Information Leaflets 1–7).

Pregnancy: radioiodine is not given to pregnant patients. Pregnancy must be avoided for 6 months after radioiodine remnant ablation (RRA) 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 until after a subsequent pregnancy.

21.6. Follow-up

Follow-up of patients with thyroid cancer is lifelong and usually supervised by specialists in secondary or tertiary care who are members of the MDT. Low-risk cases who have completed their treatment, are shown to be free of disease and no longer judged to require TSH suppression, may be followed up in settings other than the multidisciplinary 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 *Levothyroxine treatment:* The dose of levothyroxine is usually higher than a normal replacement dose as it is intended to suppress the level of serum TSH to <0.1 mU/l. 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, preferably an endocrinologist. 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 (Chapter 11.2) to ensure that hypercalcaemia does not occur. The dose is kept to the minimum required to maintain serum calcium in the (low) normal range.

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.

References

1 International Atomic Energy Agency (1991) International Criteria in a Nuclear or Nuclear Radiation Emergency. Safety Series 109. IAEA, Vienna.

2 International Commission on Radiological Protection (1991) Principles for Intervention for Protection of the Public in a Radiological Emergency. ICRP publication 63. Pergamon Press, Oxford.

APPENDIX 1

Assay methodology

1. 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 published.[1] Problems with Tg assays have been widely reviewed.[1–10] Antibodies to thyroglobulin (TgAb) may be present in up to 20% of patients with DTC.[4] These antibodies can interfere in immuoassays for thyroglobulin to produce spurious results that may be falsely elevated (radioimmunoassay) or falsely undetectable (immuometric assays). Most routine laboratories in the UK will use immunometric assays thus TgAb interference may result in inappropriate clinical inaction. In addition to interference from endogenous TgAb, interference in Tg assays due to heterophilic antibody interference is well described.[8,9,11–13]

It is essential that all laboratories have a procedure in place to identify possible assay interference.

i It is recommended that one of the following procedures is adopted:
   a In all samples, TgAb should be measured by a sensitive quantitative method simultaneously with measurement of serum Tg. If TgAb is detectable it is likely that the Tg result is unreliable **(4, D).**
   b In all samples measure Tg by both immuometric assay and radioimmuoassay. Discordant results are highly suggestive of assay interference from TgAb or heterophilic antibodies and in such circumstances neither result may be reliable **(4, D).**

ii Assay stability is required for the long term follow up of patients with differentiated thyroid cancer. If a change of method is necessary it should be planned to allow double reporting for a period of time sufficient to allow comparison and familiarity with the new assay **(4, D).**

iii There should be clear guidance from each laboratory to its users on specimen requirements and sample stability **(4, D).**

iv The use of the Community Bureau of Reference Standard for Tg (CRM 457, BCR® 457 European Commission, Institute for Reference Materials and Methods) is recommended **(4, D).**

v 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 Tg[1] **(4, D)**.

vi Patients with detectable but very low concentrations of Tg are likely to be identified using sensitive Tg assays. The clinical significance of such findings are unclear and it is recommended that serial measurements are undertaken to confirm the increase and/or a rising trend in Tg measurements before concluding there is disease recurrence[14,15] **(2+, C).**

vii A post-rhTSH serum Tg of ≥2 μg/l has been suggested as a positive response justifying further investigations and treatment in patients who have undergone total thyroidectomy and ^{131}I ablation. This threshold may not be applicable for many of the currently available assays because of known differences in sensitivity, accuracy and precision[16] **(2+, C).**

viii Laboratories and manufacturers should determine and quote the minimum reporting limit of their assay based on functional sensitivity derived from between batch precision of measurement of patient samples or pools. Limit of the blank, limit of detection and limit quantitation may also be helpful in defining analytical sensitivity (Clinical and Laboratory Standards Institute document EP17-A2) **(4, D).**

ix Laboratories and manufacturers should identify the analytical range of their Tg assay and adopt procedures to identify samples suffering from 'hook' effects[12] **(4, D).**

x 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) **(4, D).**

xi Laboratories should establish a protocol for the investigation of possible endogenous TgAb interference. Approaches may include measurement of TgAb using a sensitive assay, or discordance between Tg results obtained using immunometric assay and radioimmunoassay (RIA)[7] **(2+, D).**

xii Tg results that are inconsistent with the clinical picture merit further investigation by the laboratory. This may include measurement of Tg by alternative methods, linearity checks and or treatment with heterophilic antibody blocking tubes[12] **(2+, C).**

xiii It is desirable for the laboratory to store samples until receipt of a follow up sample to facilitate further laboratory investigations if required **(4, D).**

xiv 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 **(4, D).**

xv Laboratories should run internal quality control samples, which encompass the range of results reported. A sample with a Tg concentration close to the lower reporting limit should be run with each assay to ensure that the quoted assay sensitivity is being achieved. Laboratories should also confirm assay performance between reagent lots to ensure the long term stability of their assay (**4, D**).

xvi Laboratories should participate in an external quality assessment scheme from an accredited provider (**4, D**).

xvii Requesting clinicians should contact the laboratory before the collection of blood for Tg/TSH from patients post-radioiodine administration. The handling and transport of such radioactive samples are covered by legislation and such samples may not be accepted by the laboratory (**4, D**).

1.1. Measurement of TgAb

Serum TgAb assays show poor concordance and different assays cannot be used interchangeably.[17–20]

i TgAb should be measured in the same sample as serum Tg using a sensitive immunoassay rather than a haemaglutination method[1] (**4,D**).

ii The use of the assay analytical sensitivity may be preferable to the manufacturers' cut-off or reference range when classifying samples as TgAb negative or positive. The use of the latter, which are derived from the investigation of autoimmunity, have been shown to decrease identification of the presence of TgAb and their interference in Tg assays[18] (**2+, D**).

1.2. Measurement of Thyroglobulin in fine needle aspirate washout fluid

Measurement of tumour markers in cyst fluid[21] can be subject to matrix effects.

i Before applying a thyroglobulin immunoassay which is validated for use in serum to fine needle aspirate washout fluid, the laboratory must ensure that the method has been fully validated for use with this matrix. A protocol specifying the collection conditions (collection fluid and volume) should be agreed between clinician and laboratory before samples are collected (**4, D**).

ii Non-serum samples tested with serum tumour marker assays should always be subjected to additional quality-assessment measures, such as serial dilutions (to ensure linear dilution and confirm that the sample is not affected by the hook affect) and spike recovery experiments[20] (**4,D**).

2. Measurement of calcitonin

The C-cells of the thyroid secrete calcitonin, a 32-amino acid polypeptide which is an excellent tumour marker for MTC. The following recommendations apply to its measurement:

2.1. Method selection

i Two-site two-step immunometric assays that are highly specific for monomeric calcitonin are now preferred and have largely replaced less analytically specific radioimmunoassays[22] (**4, C**).

ii Assays should be standardized against WHO International Standard IS 89/620 (**4, C**).

iii The same calcitonin method should be used as an aid to diagnosis and for long-term follow-up of patient with MTC to ensure comparability of results. If a change of method is necessary it should ideally be planned to allow re-baselining of results with the new assay. In practice this is likely to be feasible only if assayed patient specimens are stored below −30 °C for at least a year (**4, D**).

2.2. Specimen type and stability

iv There should be clear guidance available from each laboratory to its users on specimen requirements and sample stability (**4, C**).

v Serum or plasma requirements should be confirmed with laboratories and/or manufacturers' kit inserts. The effect of gel tubes should be known (**4, C**).

vi Calcitonin in serum or plasma is unstable and blood specimens should be kept on ice. Red cells should then be separated within 30 min of collection and serum or plasma frozen immediately (**4, C**).

vii Calcitonin results may be affected by visible haemolysis or lipaemia and assay of such specimens should be avoided if possible (**4, C**).

2.3. Specimen timing

viii A specimen for calcitonin should always be taken as part of the pre-operative work-up (**4, C**).

ix 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 (**4, D**).

x The diagnosis of MTC relies on the demonstration of raised calcitonin (>90 ng/l) in the basal state. Stimulation tests using intravenous pentagastrin (0·5 mg/kg) and/or calcium infusion (2 mg/kg) are rarely used now, particularly for diagnosis, both because assays are more clinically specific and because of the lack of availability of pentagastrin. Ultrasensitive calcitonin assays (with 5 ng/l threshold) reduce the false-negative rate of basal calcitonin measurements when diagnosing familial MTC and in post-operative follow-up compared with previously used assays. However the sensitivity to detect C-cell disease remains lower than that of the pentagastrin stimulation test.[23] Provocative testing is sometimes used in follow-up, for example where basal calcitonin remains within the reference interval but progression is suspected.[24] Samples are usually collected 5 min prior to administration of calcium/pentagastrin and then at intervals of 2, 5 and 7–10 min after. Increases over baseline may be more than twice as much for calcium gluconate than those for pentagastrin requiring different cut-offs.[3,25](**4, D**).

xi Post-operative samples should be collected no earlier than 15 days after thyroidectomy, and may be misleading for up to 3 months post-operatively. Fasting samples are preferable[1,26,27] (**3, B**).

xii Calcitonin should be measured at six-monthly intervals post-operatively with less frequent measurements (e.g. every 12–18 months) sufficient in patients defined as disease-free

or if undetectable or within the normal range for 5 years and more frequent measurements desirable if the level is rising. Doubling times may also be helpful, with doubling times <6 months a poor prognostic factor.[21,26,28]

2.4. Analytical requirements

xiii Laboratories and manufacturers should determine and quote the minimum reporting limit of their assay based on functional sensitivity derived from between-batch precision of measurement of patient samples or pools. An ultrasensitive assay may be considered to be one with 5 ng/l functional sensitivity[22] **(4, D).**

xiv Laboratories should have established protocols for identifying specimens that may have 'hooked' and those that may contain interfering antibodies[12] **(4, C).**

xv Laboratories should run internal quality controls at concentrations appropriate for the range of results obtained. A pool of calcitonin concentration close to the minimum reporting limit should be included to ensure good baseline security **(4, C).**

xvi Laboratories should participate in a recognised and accredited external quality assessment scheme **(4, C).**

2.5. Clinical interpretation

i Chronic kidney disease and renal hyperparathyroidism may increase basal calcitonin levels.[29] Mildly increased calcitonin may be observed in pregnancy, pernicious anaemia, autoimmune thyroid disease, hypergastrinaemia and during the neonatal period. Relatively low serum calcitonin levels do not necessarily exclude progressive and/or metastatic disease.

ii The results of a clinical assessment of assay performance of the calcitonin method used should be available, including clinical sensitivity and specificity (i.e. positive and negative predictive values) **(4, C).**

iii Increases in calcitonin during follow-up should be confirmed with a repeat specimen to ensure the increase is not transient **(4, D).**

iv Previous treatment with monoclonal antibodies should be noted because of the potential for interference with human anti-mouse antibodies in immunometric assays **(4, D).**

v Calcitonin levels may not be a reliable marker of tumour response in patients receiving RET inhibitor therapy (e.g. Vandetanib)[30] **(4, D).**

3. Measurement of carcinoembryonic antigen (CEA)

The C-cells secrete carcinoembryonic antigen (CEA), a approximately 200 000 kDa glycoprotein which is an excellent tumour marker for MTC. The following recommendations apply to its measurement.

3.1. Method selection

i Two-site immunometric assays are usually used and have largely replaced radioimmunoassays **(4, D).**

ii Assays should be standardized against WHO International Reference Preparation 73/601 **(4, D).**

iii The same CEA method should be used as an aid to diagnosis and for long-term follow-up of patient with MTC to ensure comparability of results. If a change of method is necessary it should ideally be planned to allow re-baselining of results with the new assay. In practice this is likely to be feasible only if assayed patient specimens are stored below −30 °C for at least a year **(4, D).**

3.2. Specimen type and stability

i CEA is generally reasonably stable in serum or plasma and no particular precautions are necessary provided specimens are assayed within 3–4 days of collection. If measurement is delayed the serum or plasma should be stored below −30 °C prior to assay **(4, D).**

ii Serum or plasma requirements should be confirmed with laboratories and/or manufacturers' kit inserts. The effect of gel tubes should be known. **(4, D).**

iii CEA results may be affected by visible haemolysis or lipaemia and assay of such specimens should be avoided if possible. **(4, D).**

3.3. Specimen timing

There are no specific timing requirements for CEA measurement.

i A specimen for CEA should always be taken as part of the pre-operative work-up **(4, D).**

ii Post-operative samples should be collected no earlier than 10 days after thyroidectomy with delay until 2–3 months following surgical treatment recommended by some[27] **(3, B).**

iii CEA should be measured at six-monthly intervals post-operatively with less frequent measurements (e.g. every 12–18 months) sufficient in patients defined as disease-free or if undetectable or within the normal range for 5 years and more frequent measurements desirable if the level is rising. Doubling times may also be helpful, with doubling times <6 months a poor prognostic factor[21,26,27] **(3, B).**

3.4. Analytical requirements

i Laboratories and manufacturers should determine and quote the minimum reporting limit of their assay based on functional sensitivity derived from between-batch precision of measurement of patient samples or pools **(4, D).**

ii Laboratories should have established protocols for identifying specimens that may have 'hooked' and those that may contain interfering antibodies[12] **(4, D).**

iii Laboratories should run internal quality control at concentrations appropriate for the range of results obtained. A pool of CEA concentration close to the minimum reporting limit should be included to ensure good baseline security **(4, D).**

iv Laboratories should participate in a recognised and accredited external quality assessment scheme **(4, D).**

3.5. Clinical interpretation

CEA may be raised in a number of non-malignant conditions (e.g. irritable bowel syndrome, jaundice, hepatitis, chronic renal failure, pleural inflammation) as well as in other malignancies (e.g. colorectal, breast, gastric, lung, mesothelioma, oesophageal, pancreatic)[31] and is of most value in follow-up. Relatively low serum CEA levels do not necessarily exclude progressive and/or metastatic disease.

i The results of a clinical assessment of assay performance of the CEA method used should be available, including clinical sensitivity and specificity (i.e. positive and negative predictive values) **(4, D)**.

ii Increases in CEA during follow-up should be confirmed with a repeat specimen to ensure the increase is not transient **(4, D).**

iii Previous treatment with monoclonal antibodies should be noted because of the potential for interference with human anti-mouse antibodies in immunometric assays **(4, D).**

References

1 Association of Clinical Biochemistry, British Thyroid Association & British Thyroid Foundation (2006) *UK Guidelines* for the Use of Thyroid Function Tests. ACB, London.

2 Mazzaferri, E.L., Robbins, R.J., Spencer, C.A. *et al.* (2003) A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism*, **88**, 1433–1441.

3 Demers, L.M. & Spencer, C.A. (2003) Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease. National Academy of Clinical Biochemistry, Washington, DC. www.aacc.org/NR/rdonlyres/F343F1C7-8DFB-4718-A912030550E087A3/0/3e_thyroid.pdf.

4 Spencer, C.A., Bergoglio, L.M., Kazarosyan, M. *et al.* (2005) Clinical impact of thyroglobulin (Tg) and Tg autoantibody method differences on the management of patients with differentiated thyroid carcinomas. *Journal of Clinical Endocrinology and Metabolism*, **90**, 5566–5575.

5 Spencer, C.A. (2004) Challenges of serum thyroglobulin (Tg) measurement in the presence of Tg autoantibodies. *Journal of Clinical Endocrinology and Metabolism*, **89**, 3702–3704.

6 Stockigt, J.R. (2005) Ambiguous thyroglobulin assay results in the follow-up of differentiated thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism*, **90**, 5904–5905.

7 Weightman, D.R., Mallick, U.K., Fenwick, J.D. *et al.* (2003) Discordant serum thyroglobulin results generated by two classes of assay in patients with thyroid carcinoma: correlation with clinical outcome after 3 years of follow-up. *Cancer*, **98**, 41–47.

8 Clark, P. & Franklyn, J. (2012) Can we interpret serum thyroglobulin results? *Annals of Clinical Biochemistry*, **49**, 313–322.

9 Clark, P.M. (2009) Laboratory services for thyroglobulin and implications for monitoring of differentiated thyroid cancer. *Journal of Clinical Pathology*, **62**, 402–406.

10 Spencer, C.A. & Lopresti, J.S. (2008) Measuring thyroglobulin and thyroglobulin autoantibody in patients with differentiated thyroid cancer. *Nature Clinical Practice Endocrinology & Metabolism*, **4**, 223–233.

11 Giovanella, L. & Ghelfo, A. (2007) Undetectable serum thyroglobulin due to negative interference of heterophile antibodies in relapsing thyroid carcinoma. *Clinical Chemistry*, **53**, 1871–1872.

12 Sturgeon, C.M. & Viljoen, A. (2011) Analytical error and interference in immunoassay: minimizing risk. *Annals of Clinical Biochemistry*, **48**, 418–432.

13 Spencer, C., Fatemi, S., Singer, P. *et al.* (2010) Serum Basal thyroglobulin measured by a second-generation assay correlates with the recombinant human thyrotropin-stimulated thyroglobulin response in patients treated for differentiated thyroid cancer. *Thyroid*, **20**, 587–595.

14 Castagna, M.G., Tala Jury, H.P., Cipri, C. *et al.* (2011) The use of ultrasensitive thyroglobulin assays reduces but does not abolish the need for TSH stimulation in patients with differentiated thyroid carcinoma. *Journal of Endocrinological Investigation*, **34**, e219–e223.

15 Schlumberger, M., Hitzel, A., Toubert, M.E. *et al.* (2007) Comparison of seven serum thyroglobulin assays in the follow-up of papillary and follicular thyroid cancer patients. *The Journal of Clinical Endocrinology and Metabolism*, **92**, 2487–2495.

16 Iervasi, A., Iervasi, G., Ferdeghini, M. *et al.* (2007) Clinical relevance of highly sensitive Tg assay in monitoring patients treated for differentiated thyroid cancer. *Clinical Endocrinology*, **67**, 434–441.

17 Krahn, J. & Dembinski, T. (2009) Thyroglobulin and anti-thyroglobulin assays in thyroid cancer monitoring. *Clinical Biochemistry*, **42**, 416–419.

18 Pickett, A.J., Jones, M. & Evans, C. (2012) Causes of discordance between thyroglobulin antibody assays. *Annals of Clinical Biochemistry*, **49**, 463–467.

19 Spencer, C., Petrovic, I. & Fatemi, S. Current thyroglobulin autoantibody (TgAb) assays often fail to detect interfering TgAb that can result in the reporting of falsely low/undetectable serum Tg IMA values for patients with differentiated thyroid cancer.

20 Taylor, K.P., Parkington, D., Bradbury, S. *et al.* (2011) Concordance between thyroglobulin antibody assays. *Annals of Clinical Biochemistry*, **48**, 367–369.

21 Boot, C.S., Mahon, B.S., Bramhall, S.R. *et al.* (2010) Validity of carcinoembryonic antigen and carbohydrate antigen 19-9 measurements in pancreatic cyst fluid with a serum-based immunoassay. *Clinical Chemistry*, **56**, 1351–1352.

22 Wells, S.A. Jr, Pacini, F., Robinson, B.G. *et al.* (2013) Multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma: an update. *The Journal of Clinical Endocrinology and Metabolism*, **98**, 3149–3164.

23 Pina, G., Dubois, S., Murat, A. *et al.* (2013) Is basal ultrasensitive measurement of calcitonin capable of substituting for the pentagastrin-stimulation test? *Clinical Endocrinology*, **78**, 358–364.

24 Camacho, C.P., Lindsey, S.C., Melo, M.C. *et al.* (2013) Measurement of calcitonin and calcitonin gene-related peptide mRNA refines the management of patients with medullary thyroid cancer and may replace calcitonin-stimulation tests. *Thyroid*, **23**, 308–316.

25 Lorenz, K., Elwerr, M., Machens, A. *et al.* (2013) Hypercalcitoninemia in thyroid conditions other than medullary thyroid carcinoma: a comparative analysis of calcium and pentagastrin stimulation of serum calcitonin. *Langenbeck's Archives of Surgery/Deutsche Gesellschaft fur Chirurgie*, **398**, 403–409.

26 Fugazzola, L., Pinchera, A., Luchetti, F. *et al.* (1994) Disappearance rate of serum calcitonin after total thyroidectomy for med-

ullary thyroid carcinoma. *International Journal of Biological Markers*, **9**, 21–24.
27 Elisei, R. & Pinchera, A. (2012) Advances in the follow-up of differentiated or medullary thyroid cancer. *Nature Reviews. Endocrinology*, **8**, 466–475.
28 NCCN Guidelines Version 2.2013. Thyroid Carcinoma, 2013.
29 Schneider, R., Schaumburg, J.E., Bartsch, D.K. *et al.* (2013) The calcitonin levels can sometimes mislead parathyroid surgeons in patients with chronic kidney disease and renal hyperparathyroidism: report of a case. *Surgery Today*, **43**, 429–433.
30 Wells, S.A. Jr, Gosnell, J.E., Gagel, R.F. *et al.* (2010) Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. *Journal of Clinical Oncology*, **28**, 767–772.
31 Sturgeon, C.M., Lai, L.C. & Duffy, M.J. (2009) Serum tumour markers: how to order and interpret them. *BMJ (Clinical Research ed.)*, **339**, b3527.

APPENDIX 2

Recognition of MEN3 (MEN2B)

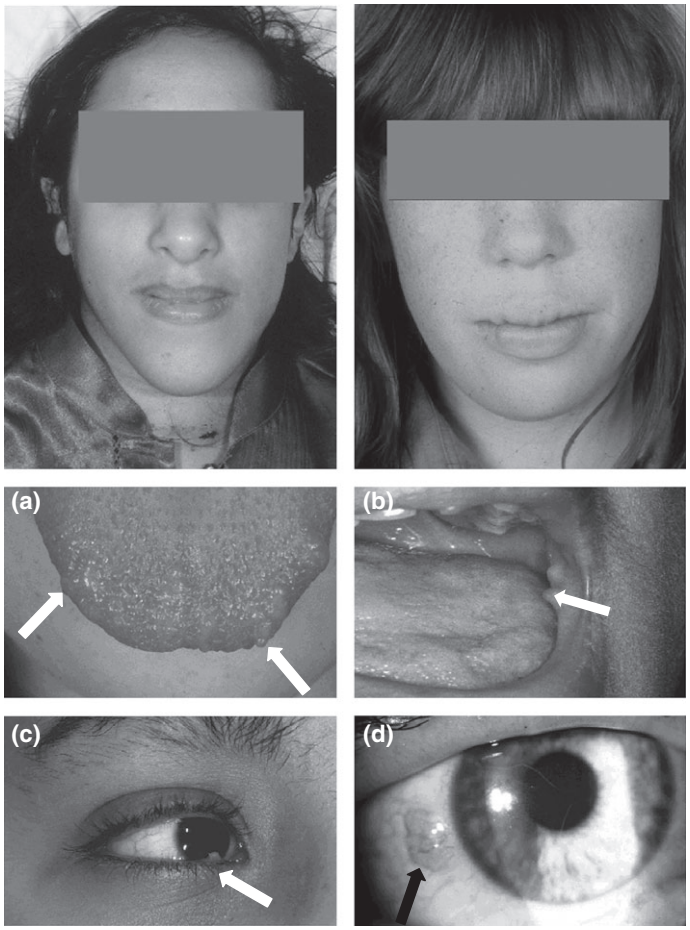


Fig. A2. Clinical features of MEN3 (previously MEN2B). Top two panels show facial appearance of two different patients. Bottom four panels: (a) and (b) neuromas on tongue and buccal mucosa, and irregular dentition (arrows) and high arch palate; (c) and (d) neuromas on eyelid, and conjunctival neuromas (arrows) and thickened corneal nerves on slit-lamp examination. (Reproduced with the consent of the patients.)

APPENDIX 3

Search methodology

Literature searches were carried out on a number of databases and worldwide web resources. The electronic literature searches included:

Cochrane Database of Systematic Reviews – CDSR (Cochrane reviews) Database of Abstracts of Reviews of Effects – DARE (other reviews) Cochrane Central Register of Controlled Trials – CENTRAL (clinical trials) Health Technology Assessment (HTA) database (technology assessments) MEDLINE/MEDLINE In-Process EMBASE – CINAHL (Cumulative Index to Nursing and Allied Health Literature).

Limits: Papers published from 2006 to 2012, human studies, English language, adult (>16 years), except for chapter on childhood cancer.

The search included the following items:

differentiated thyroid cancer; thyroid neoplasm; thyroid nodule; papillary thyroid cancer, follicular thyroid cancer, oncocytic thyroid cancer, hürthle cell carcer; medullary thyroid cancer; men2; tyrosine kinase inhibitors and medullary thyroid cancer; genetic counseling and medullary thyroid cancer; medullary thyroid cancer and surgery; medullary thyroid cancer and surgery and prophylactic; medullary thyroid carcinoma surgery and prophylactic, medullary thyroid cancer and surgery and risk reduction; medullary thyroid carcinoma surgery and risk reduction; pregnancy and medullary thyroid cancer; pregnancy and multiple endocrine neoplasia type 2; medullary thyroid cancer and genetic counseling; medullary thyroid cancer and screening; medullary thyroid cancer and ret mutations; thyroid cancer and pregnancy; thyroid cancer and radioiodine; thyroid cancer and surgery; thyroid cancer and tsh suppression therapy; thyroid cancer and diagnosis in pregnancy; thyroid cancer and conception; pregnancy and thyroxine dose adjustment; management and sialadenitis and radioiodine; timing and follow up and radioiodine scan; diagnostic radioiodine scan; empirical and radioiodine and thyroid cancer outcome and post pubertal children and thyroid cancer; thyroid cancer and radiotherapy; thyroid cancer and imr; thyroid cancer and external beam; radioiodine ablation and therapy for dtc; thyroid cancer and radioiodine; thyroid cancer and radioiodide; thyroid cancer and remnant ablation; thyroid cancer and tsh and radioiodine; thyroid cancer and low iodine diet; thyroid cancer and radioiodine and pregnancy; radioiodine and fertility; radioiodine and breast feeding; radioiodine and dosimetry; radioiodine and radiation protection; radioiodine therapy; radioiodine dosimetry; metastatic thyroid cancer; iodine refractory; recombinant tsh; tyrosine kinase inhibitors and thyroid cancer. mek inhibitors and thyroid cancer; redifferentiation and thyroid cancer; retinoids and thyroid cancer; anti-vegfr and thyroid cancer; anti-angiogenesis and thyroid cancer; braf and tyrosine kinase inhibitors; thyroid cancer and paediatrics; recombinant tsh and paediatrics; radioiodine and children; anaplastic thyroid cancer; external beam radiotherapy and anaplastic thyroid carcinoma; chemotherapy and anaplastic thyroid carcinoma; vascular disrupting agents and anaplastic thyroid carcinoma; anti-vegfr and anaplastic thyroid carcinoma; combretastatin and thyroid lymphoma; thyroid lymphoma; diffuse large b cell lymphoma and thyroid; malt and thyroid; differentiated thyroid cancer and recurrence; differentiated thyroid cancer and recurrent disease; thyroid cytology and follicular lesion; thyroid cytology and follicular neoplasm; incidence and thyroid cancer; epidemiology and thyroid cancer; incidence thyroid cancer uk; survival and thyroid cancer; familial non-medullary thyroid cancer; serum thyroglobulin and thyroid cancer; multidisciplinary team and thyroid cancer; thyroid cytology and classification; thyroid nodules and ultrasound/sonography/us, thyroid nodules and classification; thyroid nodules and malignancy; thyroid cancer and radioiodine and follow up thyroid cancer and pet-ct; benign thyroid nodule; malignant thyroid nodules; ultrasound differentiation and benign thyroid nodule; ultrasound differentiation and malignant thyroid nodule; ultrasound criteria and thyroid nodule; nuclear medicine and isotope and thyroid nodule; nuclear medicine and isotope and thyroid cancer; papillary thyroid microcarcinoma and prognosis; medullary thyroid microcarcinoma and prognosis; thyroid cytology and follicular lesion; thyroid cytology and follicular neoplasm; thyroid cytology and classification; recurrent thyroid cancer and surgery; recurrent thyroid cancer and surgery and central neck; recurrent thyroid cancer and surgery and lymph nodes; hypocalcaemia and thyroidectomy; hypocalcaemia and thyroidectomy and central neck; hypocalcaemia and thyroidectomy and central neck and lymph nodes; paediatric and thyroid cancer; paediatric and thyroid cancer and surgery; paediatric and thyroid cancer and surgery and radio-iodine; paediatric and thyroid cancer and surgery and 131iodine; childhood and thyroid cancer; childhood and thyroid cancer and surgery; childhood and thyroid cancer and surgery and radio-iodine; childhood and thyroid cancer and surgery and ^{131}iodine; i-131 and whole body scintigraphy and thyroid cancer; i-123 and whole body scintigraphy and thyroid cancer; i-131 and thyroglobulin and thyroid cancer; i-131 spect ct and thyroid cancer; i-123 spect ct and thyroid cancer; stimulated thyroglobulin and i-131 scintigraphy and thyroid cancer; neck ultrasound and thyroid cancer; neck mri and thyroid cancer; i-131 and renal failure; i-131 and thyroid cancer; i-123 and thyroid cancer; in-111 somatostatin receptor scintigraphy and thyroid cancer; tc-99m mibi and thyroid cancer; tc-99m pentavalent dmsa and thyroid cancer; management and sialadenitis and radioiodine; timing and follow up and radioiodine scan / diagnostic radioiodine scan; empirical and radioiodine and thy-

roid cancer; outcome and post pubertal children and thyroid cancer; radiotherapy; imrt; thyroid; cancer; external beam; radioiodine, radioiodide; remnant ablation; tsh and radioiodine; low iodine diet; external beam radiotherapy and anaplastic carcinoma; chemotherapy and anaplastic carcinoma; vascular disrupting agents and anaplastic carcinoma; anti-vegfr and anaplastic carcinoma; combretastatin

Additional searches to include publications in 2013 were performed during the editing phase.

APPENDIX 4

Patient information

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

1. Patient organisations offering information and support to patients

Butterfly Thyroid Cancer Trust

Butterfly Thyroid Cancer Trust is the first registered charity in the UK dedicated solely to the support of people affected by thyroid cancer.

BCTC has produced the first ever comprehensive patient information film about thyroid cancer: *Thyroid Cancer Uncovered: A Patient's Guide*. The film is a comprehensive step by step guide about the disease and treatment from diagnosis to long term follow-up. Its chapters are presented by leading UK thyroid cancer clinicians. We also follow four patient journeys. The film has been endorsed by the BAETS, British Thyroid Association, British Thyroid Foundation, A.M.E.N.D., TCSG Wales, Hypopara UK, Thyroid Cancer Support Ireland and the Thyroid Cancer Alliance. The DVD is free to all UK patients, please ask your Thyroid Cancer Care Team for a copy or contact Butterfly at: www.butterfly.org.

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

British Thyroid Foundation

The British Thyroid Foundation is a charity dedicated to supporting people with all thyroid disorders and helping their families and people around them to understand the condition.

Address: 2nd Floor, 3 Devonshire Place, Harrogate, West Yorkshire GH1 4AA
Tel: 01423 709707/709448
Website: www.btf-thyroid.org
Email: info@btf-thyroid.org

Thyroid Cancer Support Group – Wales

Supporting thyroid cancer patients and families not only in Wales but nationally and occasionally internationally. The group is funding the first national tissue bank specifically for research into anaplastic thyroid cancer.

Address: 'Morcote', Sunlea Crescent, New Inn, Pontypool, Gwent, South Wales NP4 8AD
Tel: 0845 009 2737
Website: www.thyroidsupportwales.co.uk
Email: thyroidgroup@tiscali.co.uk

Association for Multiple Endocrine Neoplasia Disorders – AMEND

AMEND provides information and support to families with multiple endocrine neoplasia (MEN) and associated endocrine tumours, including medullary thyroid cancer.

Address: The Warehouse, Draper Street, Tunbridge Wells, Kent TN4 0PG
Tel: 01892 516076
Website: www.amend.org.uk
Email: info@amend.org.uk

Hypopara UK

Hypopara UK is the national patient organisation for people with parathyroid conditions, including post-surgical calcium issues and permanent hypoparathyroidism.

Address: 6 The Meads, East Grinstead, West Sussex RH19 4DF
Tel: 01342 316315
Website: www.hypopara.org.uk
Email: info@hypopara.org.uk

2. Other sources of information for patients

Macmillan Cancer Support

www.macmillan.org.uk

Cancer Research UK

http://www.cancerresearchuk.org/

Thyroid Cancer Support Ireland

http://www.thyroidcancersupport.ie/

American Thyroid Association (information for patients from the ATA)

http://www.thyroid.org/patient-thyroid-information/

MedlinePlus (information for patients from the US National Library of Medicine)

www.medlineplus.gov

Pubmed (search the medical literature)

www.ncbi.nlm.nih.gov/pubmed

Thyroid-cancer.net (information for patients from the Johns Hopkins thyroid tumor center)

www.thyroid-cancer.net

Thyroid Cancer Alliance

www.thyroidcanceralliance.org

Thyroid Federation International

www.thyroid-fed.org/

Disclaimer

Whilst every care is taken in compiling this list, the British Thyroid Association IS not responsible for the information provided by the organisations listed here or for the content of third party websites.

Revised February 2014

PATIENT INFORMATION 1

British Thyroid Association Patient Information Leaflet 1: The thyroid gland and thyroid cancer – tests and treatment

What is the thyroid gland?

The thyroid gland is an endocrine gland and makes hormones, which are released into the bloodstream. These hormones affect cells and tissues in other parts of the body and help them to function normally.

Where is the thyroid gland?

The thyroid gland is at the base of the neck. It is made up of two lobes (each about half the size of a plum). 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 that are released into the bloodstream:

- thyroxine (T4);
- triiodothyronine (T3); and
- calcitonin, which has no known action in healthy people. Raised levels of calcitonin may indicate the presence of medullary thyroid cancer (MTC).

(For more information see the British Thyroid Association Patient Leaflet – Medullary Thyroid Cancer.)

T4 and T3 can both be replaced by medication, and the body can function perfectly well with little or no calcitonin.

What do the thyroid hormones do?

Thyroid hormones (T3 and T4) help to control the speed of body processes – your metabolic rate. In the body, T4 is converted into T3 which is the active hormone which influences the way cells and tissues work. If too much thyroid hormone is released, your body works faster than normal and you have 'hyperthyroidism'. This would make you feel overactive and anxious, hungrier than usual, and you would lose weight. However, if too little of the thyroid hormones is produced, your body works slower than normal and you have 'hypothyroidism'. In that case, you would feel tired and sluggish, and put on weight easily.

How is the thyroid gland controlled?

The thyroid is controlled by the pituitary gland, 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 releasing a hormone called thyroid stimulating hormone (TSH). TSH stimulates the thyroid gland to produce more T3 and T4. If the thyroid hormone levels rise above normal levels, the pituitary senses this and stops releasing TSH and so the thyroid gland will produce less T3 and T4.

How is thyroid activity measured?

Your doctor will start by taking a history of your symptoms and by a physical examination. You will also be asked to give a small sample of blood, which will be analysed in the laboratory to show how much T4, T3 and TSH are being produced. These tests are sometimes called thyroid function tests or TFTs.

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

Near your thyroid gland are four tiny parathyroid glands, each the size of a pea. They are not related to the thyroid except by name – 'para' comes from the Greek for 'near'.

Parathyroid glands release a hormone called parathyroid hormone (PTH) which helps to regulate calcium, phosphate and magnesium levels. Calcium levels need regulating because they fluctuate constantly in response to a number of factors such as food, drink, exercise, stress, infection, and other medications.

Calcium is an important mineral because it is in every cell of the body. It affects bones, nerves, muscles, heart rhythm and cell function as well as your emotions. Levels must therefore be kept stable to make sure your body functions correctly.

The parathyroid glands regulate calcium levels by means of a feedback mechanism. They continually monitor the amount of calcium in your blood as it passes through them and they make constant adjustments by releasing just enough PTH to keep your levels stable.

Sometimes the parathyroid glands may be temporarily affected by surgery and stop producing enough PTH. In some cases this may be permanent. Without enough parathyroid hormone calcium levels become too low. This condition is called hypoparathyroidism. Low calcium (hypocalcaemia) causes a range of symptoms, so if the parathyroids are permanently damaged, you will need to take medication for life and to have regular blood tests.

Thyroid cancer

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

There are several different types:

- Papillary thyroid cancer – this is the most common thyroid cancer. It is more common in younger people, particularly women.
- Follicular thyroid cancer – this is less common, and tends to occur in slightly older people than those with papillary cancer.
- Medullary thyroid cancer – this is a rare type of thyroid cancer, which is sometimes hereditary (i.e., it is passed down through a family from one generation to the next).
- Anaplastic thyroid cancer – a rare and aggressive form of thyroid cancer which occurs most often in people over 60.

Thyroid cancer can be 'differentiated' or 'undifferentiated'. 'Differentiated' means the cancer cells still look like normal thyroid cells in appearance. They do not spread as rapidly as the undifferentiated type of cancer cells. 'Undifferentiated' cells look very different from normal thyroid cells. Papillary and follicular thyroid cancers are both differentiated. Anaplastic thyroid cancer is undifferentiated. There are several less common variants of differentiated thyroid cancer, such as Hurthle cell, tall cell, insular, and columnar.

Most thyroid cancers are very treatable and curable, but it is possible that they will recur. This can occur at any stage, but recurrences can be treated successfully. Life-long follow-up is usually recommended except for some very small cancers treated with surgery alone.

What is the cause of thyroid cancer?

Exposure to radiation either in the environment or due to radiation in childhood is known to increase the risk of getting thyroid cancer. For example, after the Chernobyl accident, many more children in the area got thyroid cancer. It has also been found in people who had external radiotherapy (X-ray treatment) to the neck 10 or 20 years earlier and in people who have had radiation treatment for cancer earlier in life.

In most cases the cause the cause of thyroid cancer is unknown. Medullary thyroid cancer is sometimes hereditary (i.e. it is passed down through a family from one generation to the next). Very occasionally papillary cancer is hereditary.

What are the symptoms of thyroid cancer?

- a painless lump in the neck which gradually increases in size;
- difficulty in swallowing due to pressure of the enlarged thyroid gland on the oesophagus (gullet);
- difficulty in breathing due to pressure of the enlarged thyroid gland on the trachea (windpipe); or
- hoarseness of the voice.

Patients suspected of having medullary thyroid cancer may have some of these symptoms but they may also have diarrhoea caused by higher than normal calcitonin levels. Some patients with medullary thyroid cancer are identified through a DNA blood test.

Cancer cells do not generally affect hormone production from the thyroid, so symptoms of an over- or underactive thyroid are rare.

Often there are no symptoms, however, and it is found by chance.

What tests will I need?

If you have one of the above symptoms, you should discuss these with your GP who will usually examine your neck and arrange a blood test. If your GP thinks the lump in your neck is suspicious they will refer you either to a specialist (usually an endocrinologist or surgeon) or to a Multi-Disciplinary Team (MDT) with a special interest and expertise in thyroid cancer.

Fine needle aspiration (FNA). This is done in an outpatient hospital clinic. A very thin needle is inserted into any swelling you may have in your neck and a sample of cells is taken out. These cells are then analysed under a microscope. This may confirm that thyroid cancer is present but it cannot diagnose follicular thyroid cancer.

Blood tests. Some additional blood tests may be done to re-check the function of your thyroid and your thyroid antibody levels.

Thyroid ultrasound scan. A picture of the thyroid gland is obtained by using sound waves which will show any solid lumps or cysts. This cannot diagnose cancer on its own but it can help with the overall diagnosis and in planning treatment. A thyroid ultrasound scan can often rule out thyroid cancer.

What treatment will I be offered?

You will usually be offered surgery (thyroidectomy).

Surgery is usually the first line of treatment for thyroid cancer. Some people will have a 'hemithyroidectomy' or 'lobectomy' (half the thyroid is removed). Some people will have a total thyroidectomy (whole thyroid gland is removed). Sometimes the operation is done in two stages, a hemithyroidectomy followed by a 'completion thyroidectomy'. The type of operation depends on various factors such as the type of thyroid cancer, your age, the size of the lump and results of the tests mentioned above. If the FNA has been inconclusive you will be offered a lobectomy so that the lump can be analysed in the laboratory. If this shows that cancer is present you may be offered completion surgery to remove the other lobe in a second operation.

In some cases some of the lymph nodes in your neck will be removed at the same time.

After a thyroidectomy, you will need to take levothyroxine tablets (also known as synthetic thyroxine or T4) as prescribed for the rest of your life. You will need to have regular blood tests to check that your 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.

(For more information see the BTA Patient Leaflet – thyroid surgery.)

Following your discharge you will need to be reviewed in the outpatient clinic to check how your wound is settling down, your hormone levels and how you are feeling. When you are at home after your surgery, please contact your treatment centre or your GP if:

- you feel extremely tired;
- you have feelings of pins and needles in your hands, feet or face;
- you have palpitations;
- you feel shaky;
- you become very overactive; or
- you generally feel very unwell.

This may mean you need to have your thyroid or calcium levels checked and your medication dose may need to be increased or decreased.

Unless you have medullary thyroid cancer, or anaplastic thyroid cancer, you may need to have radioactive iodine (RAI) treatment after surgery. The purpose of RAI is to destroy any remaining thyroid cells. Your specialist will tell you if you need RAI treatment. RAI treatment is painless. It means taking either one or two capsules or as a liquid, in a single dose. For the safety of others, you need to stay in hospital for the first 2–4 days and to reduce your social contact. If you need this treatment you will be given detailed information by your specialist consultant. *(See also the BTA Patient Leaflet on radioactive iodine.)*

In the early years following RAI you will need to keep your TSH 'suppressed' (i.e. turned off). Your thyroid cancer specialist will advise on the dose and it is important that no-one else changes the dose without discussion with your specialist.

It will be particularly important to have your thyroid hormones checked as soon as it has been confirmed that you are pregnant, as you may need to increase your dose of levothyroxine by about 30%. More frequent checks on your thyroid hormone levels will be required during pregnancy.

Currently, patients in Scotland, Wales and Northern Ireland do not have to pay for their prescriptions. Patients in England taking lifelong levothyroxine or who are diagnosed with hypoparathyroidism are currently entitled to free prescriptions for all medicines. You should obtain the appropriate leaflet from your doctor who will sign it and send it on. You will then receive an exemption certificate, which you must show to your pharmacist when collecting medicines.

Most thyroid cancers are very treatable and curable. There are, however, some more aggressive forms of thyroid cancer that will need a different treatment regimen.

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

Patient support organisations

Being diagnosed with a rare cancer can make you feel isolated. Talking to others who have been through it can help. Support and information are available through the patient-led organisations mentioned below who have collaborated in writing this leaflet. Together we can give you informational and emotional support to help you through your investigations, treatment and recovery.

Association for Multiple Endocrine Neoplasia Disorders – AMEND. AMEND provides information and support to families with multiple endocrine neoplasia (MEN) and associated endocrine tumours, including medullary thyroid cancer.

Address: The Warehouse, Draper Street, Tunbridge Wells, Kent TN4 0PG
Tel: 01892 516076
Website: www.amend.org.uk
Email: info@amend.org.se.uk

British Thyroid Foundation. The British Thyroid Foundation is a charity dedicated to supporting people with all thyroid disorders and helping their families and people around them to understand the condition.

Address: 2nd Floor, 3 Devonshire Place, Harrogate, West Yorkshire GH1 4AA
Tel: 01423 709707/709448
Website: www.btf-thyroid.org
Email: info@btf-thyroid.org

Butterfly Thyroid Cancer Trust. Butterfly Thyroid Cancer Trust is the first registered charity in the UK dedicated solely to the support of people affected by thyroid cancer.

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

Hypopara UK. Hypopara UK is the national patient organisation for people with parathyroid conditions, including post-surgical calcium issues and permanent hypoparathyroidism.

Address: 6 The Meads, East Grinstead, West Sussex RH19 4DF
Tel: 01342 316315
Website: www.hypopara.org.uk
Email: info@hypopara.org.uk

Thyroid Cancer Support Group – Wales. Supporting thyroid cancer patients and families not only in Wales but nationally and occasionally internationally. The group is funding the first national tissue bank specifically for research into anaplastic thyroid cancer.

Address: 'Morcote', Sunlea Crescent, New Inn, Pontypool, Gwent, South Wales NP4 8AD
Tel: 0845 009 2737
Website: www.thyroidsupportwales.co.uk
Email: thyroidgroup@tiscali.co.uk

British Thyroid Association Patient Information Leaflet 2: Information for patients being investigated for thyroid lumps

Things you need to know before your hospital appointment

Why have I been referred? You have been found to have a lump in your thyroid gland. Such lumps are common and usually non-cancerous. You have been referred to the hospital for further tests.

What tests will I have? You will have a consultation with a doctor who will ask about your symptoms and then will examine your neck. You may require some blood tests and an ultrasound examination. A biopsy known as fine needle aspiration (FNA), may be necessary. This is similar to a blood test but taken from the lump and usually, no local anaesthetic is required. A very thin needle is inserted into any swelling you may have in your neck and a small amount of fluid is taken out. The cells in the fluid are then analysed under a microscope. The doctor will explain the procedure in detail. If you have any questions do not hesitate to ask the doctor.

The ultrasound and biopsy is usually scheduled for a later date. The doctor will explain this in more detail.

Sometimes the doctor decides that no biopsy is required and if so, the reason for that will be discussed with you during the consultation.

Before you leave the clinic, make sure that the doctor has made it clear to you *when* the result will be available and *how* you will receive that information.

Things you need to know after your biopsy

What symptoms will I have after the biopsy? You may have some discomfort in your neck, especially when you swallow. This will improve quickly. After 24 h you may have a little discomfort, and after 48 h hardly any. You can use simple pain killers such as paracetamol if needed. You may also have some bruising around the area where the needle was inserted. The bruising will clear within about a week. If the lump was mainly due to fluid then it is not unusual for the fluid to collect again over a period of 1 or more weeks. This should not alarm you, unless it is painful and red, in which case you should consult your GP.

When will I find out the result of the biopsy? It takes 1–2 weeks for the lab to examine the biopsy and issue a report. The result will be given to you at your next appointment, or if you have expressed a preference to receive it by letter or telephone, as soon as the result has become available. If you have not been notified after 3 weeks, please phone the consultant's secretary.

What are the possible outcomes of the biopsy? In most cases the biopsy result is benign (no evidence of cancer). Sometimes, the biopsy result is unhelpful, because there were not enough cells in the sample to test, or because it was not possible to decide on the significance of the cells. In such cases, the doctor may recommend repeating the biopsy, or he may advise you to have an operation to remove part of your thyroid. Approximately in one out of twenty cases the biopsy shows that the lump is cancerous.

What happens if the biopsy is benign? A benign result is highly reassuring. Rarely it may have to be repeated.

What happens if the biopsy result is suspicious or cancerous? The doctor will discuss this with you and in most cases you will require a thyroid operation to remove part or all of your thyroid gland.

If you would like further information about thyroid cancer please contact one of the patient organisations listed at the end of this leaflet.

Things you need to know after you have been discharged from the clinic

Your tests have shown no evidence of thyroid cancer, which is highly reassuring. This means that the risk of you developing thyroid cancer in future is remote and no different from anybody else.

Do I need to look out for anything in future? No more than anyone else. There are some symptoms, which should not be ignored if they occur, especially if they are persistent or are getting progressively worse. They include:

- the lump is getting bigger;
- the lump feels harder;
- a new lump develops;
- you develop difficulties swallowing or breathing;
- your voice becomes hoarse.

What should I do if I develop new symptoms? If you develop any new symptoms like those described above, you should let your GP know. In some cases your doctor may be able to reassure you. In other cases you may need to be referred to hospital for additional tests.

For further information about thyroid lumps you may contact the British Thyroid Foundation (address below) for a copy of the BTF leaflet *Thyroid Nodules and Swellings*.

Patient support organisations

The following patient-led organisations provide information and support and the chance to speak to other patients who have been through surgery and treatment for thyroid nodules including thyroid cancer.

British Thyroid Foundation. The British Thyroid Foundation is a charity dedicated to supporting people with all thyroid disorders and helping their families and people around them to understand the condition.

Address: 2nd Floor, 3 Devonshire Place, Harrogate, West Yorkshire GH1 4AA
Tel: 01423 709707/709448
Website: www.btf-thyroid.org
Email: info@btf-thyroid.org

Butterfly Thyroid Cancer Trust. Butterfly Thyroid Cancer Trust is the first registered charity in the UK dedicated solely to the support of people affected by thyroid cancer.

Address: PO Box 205, Rowlands Gill, Tyne & Wear NE39 2WX
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Tel: 0845 009 2737
Website: www.thyroidsupportwales.co.uk
Email: thyroidgroup@tiscali.co.uk

Association for Multiple Endocrine Neoplasia Disorders – AMEND. AMEND provides information and support to families with multiple endocrine neoplasia (MEN) and associated endocrine tumours, including medullary thyroid cancer.

Address: The Warehouse, Draper Street, Tunbridge Wells, Kent TN4 0PG
Tel: 01892 516076
Website: www.amend.org.uk
Email: info@amend.org.se.uk

British Thyroid Association Patient Information Leaflet 3: Surgery for thyroid cancer

What is a thyroidectomy?

Thyroidectomy is a common operation. Some patients will have half the thyroid removed (the medical terms for this are hemithyroidectomy or lobectomy), others will have the whole thyroid gland removed (the medical term for this is total thyroidectomy). Total thyroidectomy may be performed in two stages – a hemithyroidectomy followed by a 'completion thyroidectomy'.

Some patients with papillary thyroid cancer may require more extensive surgery. Total thyroidectomy may be combined with neck dissection – removal of the lymph nodes in the central (front) compartment and sometimes the lateral (side) compartment in your neck.

If medullary thyroid cancer has been diagnosed, total thyroidectomy and central lymph node dissection is routinely undertaken to remove lymph nodes. Lateral neck dissection is sometimes required.

Your surgeon will explain to you whether a part or your entire thyroid needs to be removed. They should explain the possible risks of each procedure so that you can give fully informed consent. If you do not understand any of the information you are given, please ask. It is important for you to make a choice that you are comfortable with.

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

Thyroid surgery is generally safe but there are some possible risks you need to be aware of.

Whether you are having a hemithyroidectomy or a total thyroidectomy there is a very low risk of bleeding or infection after the operation. There is also a risk of temporary voice change, which in a few cases may become permanent. Despite the surgeon's best efforts some people will have a poor neck scar.

If you are having a total thyroidectomy or neck dissection there is a risk of more significant voice change. If that happens you will be offered an examination of the vocal cords by a specialist. Occasionally breathing and swallowing difficulties can arise. Very rarely a tracheostomy (an artificial opening in the windpipe to help you breathe) may be needed. There is also a risk of a low blood calcium as a result of the parathyroid glands not working. The low calcium in the blood and need for calcium/vitamin supplements to treat this may be temporary or permanent.

A lateral neck dissection involves a longer incision. Your surgeon will explain this to you. During this procedure there is a risk of injury to an important nerve in the neck which helps with neck and shoulder function (accessory nerve). This may be temporary or permanent and can result in pain and stiffness around the shoulder.

Don't hesitate to ask your surgeon about the number of thyroid operations they perform each year, and their complication rates, and whether they are core members of the thyroid Multi-Disciplinary Team (MDT). The risk of complications is lowest if thyroid surgery is undertaken by an experienced endocrine or head-and-neck surgeon who regularly does thyroid and parathyroid surgery, preferably working as part of an MDT. Department of Health Cancer Standards require that surgeons who operate on patients with thyroid cancer should perform a minimum of 20 thyroidectomies per year.

Before the operation you will be examined by your surgeon, and may have additional tests to assess your suitability for a general anaesthetic.

Will it affect my voice?

The thyroid gland lies close to the voice box (larynx) and the nerves to the voice box. If you depend on your voice in your work or hobbies, or if you are a singer, you should discuss this with your surgeon.

Before the operation you will have a vocal cord check. A local anaesthetic may be sprayed into your nose to make the procedure as painless as possible. A thin flexible camera (endoscope) is then gently passed into one nostril and over the back of the nose into your throat.

After your surgery you may find that your voice sounds hoarse and weak, and your singing voice may be altered. The changes may be due to changes in muscle function in the neck, rarely to injury to the recurrent laryngeal nerve which causes a vocal cord palsy (reduced movement of the voice box muscle). In most cases this recovers within a year. Speech therapy may be required prior to recovery of the nerve.

Temporary voice change can occur in up to 10% of cases, but permanent injury is uncommon and happens in less than two percent of cases. If this happens, ask your surgeon about possible treatment such as speech therapy or further surgery.

Will surgery affect my calcium levels?

The thyroid gland lies close to four tiny parathyroid glands, each about the size of half a pea. They produce parathyroid hormone (PTH) that regulates levels of calcium in your blood. The calcium level in your blood will be checked after your operation.

After total or completion thyroidectomy PTH levels can fall which causes the calcium level in your blood to drop. A low calcium level in the blood (hypocalcaemia) may cause symptoms such as tingling in your lips or fingers or cramps. If you have symptoms you should tell a doctor or nurse immediately. You will have a blood test and, if low calcium is confirmed, you will be given some calcium in tablet form or through a drip in your arm.

You may need to take vitamin D and calcium tablets after the operation. In about 30% of cases this is temporary. In <10% of cases this may be permanent in which case you may require life-long vitamin D and calcium tablets. Your blood calcium will need to be monitored regularly by the hospital or by your GP. If you are left on supplements longer than 6 months ask your specialist to check your PTH level to see if it is possible to be weaned off the tablets. This is successful in many cases.

If you need long-term calcium and/or vitamin D supplements, follow-up is necessary to monitor your blood, bones and kidneys and sometimes adjustment of your medication. Your GP will care for you between hospital appointments and will organise regular blood tests, particularly during medication adjustments. Once your levels are stable you should be able to lead a normal life.

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

You may 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 they are up and walking around. After a few weeks your neck and shoulder movements should be back to normal.

If you have had more extensive neck surgery to remove some of your lymph nodes you may need to be referred to a physiotherapist.

Will I have a scar?

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

When will the operation be done?

If you have been to an outpatient clinic you 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 run a pre-admission assessment clinic to which you will be invited before your operation. This enables both the doctors and the nurses to assess your health needs and carry out the routine tests needed before surgery. Some patients may have their tests carried out the day before surgery and in that case would not be asked to attend a pre-admission assessment.

The pre-admission assessment can provide the opportunity to meet ward staff and to see where you will be admitted on the day of your operation. You can also ask questions and discuss any concerns you may have about your operation and coming into hospital.

What about smoking?

All hospitals operate a 'No Smoking' policy. Smoking is not allowed on the ward. If you do smoke, it is in your own health interests to stop smoking at least 24 h before your anaesthetic. Please contact your GP's surgery for advice on stopping smoking.

What should I bring into hospital?

The hospital will provide you with a list. This will include: nightwear, dressing gown, slippers, toiletries, things to occupy you such as books and magazines, a small amount of money, and a notebook and 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. This gives you 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 given a receipt.

Will there be a bed ready when I arrive?

If the hospital runs an emergency service, it is not always possible to predict how many beds will be available. Beds are allocated in the same sequence as the operating lists. 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.

Please feel free to ask any member of staff for help and advice at any time. Hospital staff will do their best to accommodate you and to keep you waiting for as little time as possible.

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

When you are taken to your bed, the nurse will welcome you and check your details.

You will need to wear a special theatre gown for your operation. This will be given to you by the nurse who will show you how to wear it and help you if you want.

You will also be given a pair of white elastic stockings to wear during and after the operation which will prevent blood clots from 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 will be fully unconscious for the whole operation. Removing all or part of the thyroid involves delicate surgery which means that the operation can take about 2 h.

To prevent vomiting and other complications during your operation you will be asked not to eat or drink anything for at least 6 h before your operation. You will be told what time to stop eating and drinking when you attend the pre-admission assessment or by letter from the consultant's secretary.

You should expect to be in hospital for 1–3 days, depending on the extent of surgery, or longer if any complications arise.

If you would like to talk with another patient who has had a thyroidectomy we suggest you contact one of the patient support organisations listed at the end of this leaflet before you go to hospital.

What will happen when I go to theatre?

Just before going to theatre a nurse will complete a checklist. You will then be taken 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 should be removed beforehand and given to the nurse or stored in your locker.

The anaesthetist will usually insert a small needle into the back of your hand and give you your anaesthetic through that. 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 be monitored closely during the first hours after surgery. 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.

If you have had a total or completion thyroidectomy your calcium levels will be checked. 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 h). 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 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.

Surgeons use a variety of techniques to close the wound: stitches, staples, or a pull-through single thread or 'bead'. Some surgeons spray the wound. Others cover it with a waterproof dressing.

You may have one or more wound drains from your wound to collect wound fluid which naturally occurs after your surgery. These are thin plastic tubes which are inserted into the neck at the end of your operation and attached via a long length of tubing outside the neck to a plastic bottle or bag that collects the fluid. The drains are not painful and you can carry them around with you. They will be removed by a nurse usually a day or two after your operation when there is very little fluid coming through.

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.

For your own safety it is important that you do not get out of bed on your own immediately after your operation as you may be drowsy and weak from the anaesthetic. At first when you need to use the toilet a member of staff will need to help you. You will soon be able to walk to the bathroom yourself. Most patients are up and walking around after the first day.

You will have a nurse call bell within easy reach so that you can get help from the ward staff as needed.

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.

Will I have a sore neck?

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

The painkillers should also ease the discomfort caused by swallowing. Your neck may appear swollen and hard to touch, with some numbness, which will gradually ease 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 and clean it as necessary. When

you are feeling better 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 your GP.

How should I take care of my neck wound?

When you leave hospital you will be given advice how to look after the wound. If the stitches need removing you will be given an appointment. Take care not to knock your wound and remember to dry it carefully if it becomes wet during 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. Creams such as 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.

Sometimes the scar is raised, red and itchy. Some flatten in time but others develop into keloid scars which tend to remain thickened. Vitamin E oil, topical steroid creams, and silicone gel sheeting may help. Steroid injections may be worth considering if these fail.

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 medication will I need?

The total removal of the thyroid gland means that you will need to take replacement hormone tablets called levothyroxine (T4) every day for the rest of your life, otherwise you will experience symptoms of hypothyroidism (underactive thyroid). Levothyroxine tablets are the size of a sugar sweetener and safe to take. With monitoring by your specialist centre and/or your GP you will be able to lead an active and normal life.

Levothyroxine tablets are also given to suppress the level of thyroid stimulating hormone (TSH). This is an important part of the treatment for thyroid cancer so most patients will be given levothyroxine even if they have had only part of the thyroid removed.

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 if you are thinking of starting a family do ask your specialist for advice and information first.

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. The dose of levothyroxine should NOT be altered without discussion with a member of the Joint Thyroid Cancer Clinic clinical team.

If you have had a hemithyroidectomy and no cancer is found, the remaining thyroid tissue in two out of three patients will produce sufficient thyroid hormone for your needs. In about a third of patients the remaining thyroid gland is not able to produce enough thyroid hormone. The blood tests that you will have in the follow up clinic will identify if thyroxine replacement is needed. If this is the case you will need to take levothyroxine for life.

Currently, patients in Scotland, Wales and Northern Ireland do not have to pay for their prescriptions. Patients in England taking lifelong levothyroxine or who are diagnosed with hypoparathyroidism are currently entitled to free prescriptions for all medicines. You should obtain the appropriate leaflet from your doctor who will sign it and send it on. You will then receive an exemption certificate, which you must show to your pharmacist when collecting medicines.

When should I return to work?

This depends on your occupation, the nature of your work, and how you are feeling. The hospital can issue you with a note for 2 weeks and then you should see your GP if more time off is needed.

Will I need to be checked in an outpatient department following discharge home?

Following your discharge you will need to be reviewed in the outpatient clinic to check how your wound is settling down, your hormone levels and how you are feeling. You may 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 an appointment shortly after discharge. Depending on 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?

A diagnosis of cancer can bring all sorts of mixed emotions, but you do not have to face your treatment on your own. Support and help is available from the medical and nursing staff and from patient support organisations. Together they can give you information and emotional support to help you through your investigations, treatment and recovery.

Patient support

The following patient-led organisations have collaborated in writing this leaflet. Each provides information and support and

the chance to speak to other patients who have been through surgery and treatment for thyroid cancer.

Association for Multiple Endocrine Neoplasia Disorders – AMEND. AMEND provides information and support to families with multiple endocrine neoplasia (MEN) and associated endocrine tumours, including medullary thyroid cancer.

The Warehouse, Draper Street, Tunbridge Wells, Kent TN4 0PG
Tel: 01892 516076
Website: www.amend.org.uk
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British Thyroid Foundation. The British Thyroid Foundation is a charity dedicated to supporting people with all thyroid disorders and helping their families and people around them to understand the condition.

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British Thyroid Association Patient Information Leaflet 4: Radioactive iodine ablation and therapy

Radioactive iodine (RAI) may be used to destroy any remaining thyroid tissue in the neck after a thyroid operation. This is known as 'RAI remnant ablation' (RRA). Radioiodine "therapy" is the use radioiodine to treat any thyroid cancer that is known to be left behind after surgery (for instance in the neck or lungs), or that has recurred after initial treatment.

The treatment consists of swallowing RAI usually as a capsule. RAI is used in the treatment of thyroid cancer because under normal circumstances the thyroid gland acts as an iodine store in the body. When we eat iodine in our diet it is taken up by the thyroid gland and used to make thyroid hormones and stored in the thyroid gland. This means that we can use iodine in a radioactive form to target any remaining thyroid cells and destroy them.

You will need to be admitted into hospital and stay in a specially equipped room (sometimes called the iodine suite, isotope room or isolation room) in order to receive RAI. You can ask to see the room beforehand. In some centres photos or a DVD may be available to show the room and facilities.

Is RAI treatment safe?

RAI has been used to treat thyroid cancer safely for over 60 years. There is a very small increased risk of developing a second cancer, but with people living longer, the risk of second cancers is growing for everyone. This has to be balanced against the benefits in treating the thyroid cancer. Your treatment team will discuss these issues with you before the treatment.

The precautions described below are intended to protect other people by reducing unnecessary exposure to radiation, particularly for pregnant women and young children.

Are there any side effects from RAI treatment?

Most patients do not have side effects from RAI treatment. Some patients may experience a feeling of tightness or swelling in the neck and/or feel flushed, which may last for a few days. If this happens please inform the nursing staff immediately. A simple painkiller can be given to relieve this problem. You may feel pain in the neck region shortly after having RAI, but this is rare. It can be treated very effectively with a short course of steroids tablets.

Sometimes having RAI can result in a temporary taste disturbance. This might not start until you get home. It can last for a few weeks, and usually resolves. Drinking plenty of fluids after the treatment helps to reduce this problem.

Saliva glands will also take up some of the RAI. Sometimes this can result in symptoms. In most cases this is temporary but in a few cases it may be permanent. You will be advised to drink plenty of fluids during your admission to reduce the risk of these complications as well as to speed up the clearance of the RAI from the body. Some hospitals recommend drinking a tumbler of water every waking hour to flush out the radioactivity. Some hospitals recommend either chewing gum or sucking sweets to encourage the salivary glands to keep working, but there is no evidence that this helps.

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 breastfeeding?

It is very important that you do not have RAI treatment if you are pregnant. If you are of childbearing age you will be asked about your chances of being pregnant. Blood or urine pregnancy tests can be done where there are any uncertainties.

If you are breastfeeding, you should stop this at least six and preferably eight weeks before you have the RAI treatment. You should not start again afterwards.

What about sex, contraception and fertility?

You should use a condom for seven days after RAI.

You should use a reliable form of contraception from the time of your treatment and for six months after. Female fertility should not be affected in the long term even after repeated doses of RAI.

Male patients are advised not to father children for at least four months after RAI treatment. Your fertility should not be affected in the long term, but there may be a small risk of reduced fertility if repeated RAI is needed. In this situation you can be considered for sperm banking. Please discuss this with your specialist consultant or a member of the treatment team as specialist advice and help is available.

What medication/tablets should I take before RAI?

After surgery to remove the entire thyroid gland, you will need to take thyroid hormones in tablet form. The type of tablet that you are prescribed will depend on how you are going to be prepared for your RAI treatment.

Preparing you for RAI treatment

Currently there are two regimes used in the UK to prepare for RAI.

The recommended regime is as follows:

- Following removal of your thyroid gland the thyroid hormone levothyroxine (T4) will be prescribed for you.
- Just before RAI you will be given two injections of recombinant human TSH, also known as Thyrogen™.
- Thyrogen injections will be given into the buttock on two consecutive days. On the third day you will go into hospital for the RAI treatment. You will remain on levothyroxine throughout.
  Please contact your oncology team at least one month before your planned date for RAI treatment if you are unsure about your thyroid medication and what is planned for you.

The other regime is as follows:

- Following removal of your thyroid gland thyroid hormone Liothyronine (T3) will be prescribed for you.
- T3 tablets will then be stopped two weeks before your RAI treatment.
- You may feel week and tired after you stop taking your tablets. This is normal. It will improve once you start taking levothyroxine (T4), usually a few days after you have had your RAI.
- You are advised not to drive after stopping the tablets and to wait until you are fully comfortable with this after restarting your levothyroxine tablets.
- Being without your thyroid hormone replacement may also make you feel cold, especially your hands and feet. Take some warm clothing and bed socks into hospital with you.
- You will usually be started on levothyroxine (T4) on the day you go home.
  The instructions about stopping your thyroid medication may vary in different centres. It is important you follow the instructions from your treatment team.

Should I keep taking my other medication/tablets?

If you are taking any other medication such as calcium supplements and vitamin D tablets for hypoparathyroidism or any other medication, you should carry on doing so. Please bring a small supply with you on admission and show it to the doctor and nurse team.

If you are taking any iodine-containing vitamin or mineral supplements or cod liver oil, you should stop taking them around two weeks before your therapy to help reduce your iodine levels.

What can I eat?

Some studies have shown that reducing iodine intake may improve the effectiveness of the treatment. Therefore, two weeks before coming in to hospital we recommend the following:

- You can eat fresh and frozen fruit and vegetables, fresh and frozen meats, rice, pasta and potatoes, soft drinks, fruit juices, beer, wine, tea, coffee, plain fats and oils (non-dairy), olive oil spread, fresh and homemade bread.
- Avoid eating seafood and fish, cows'/goats' milk, cheese, ice cream, yoghurt, butter, and egg yolks.
- Avoid food from restaurants, fast-food chains and takeaways, and imported processed foods. In the USA and in many European countries iodine is added to table salt and used in baking.
- Some cough mixtures and health foods (such as seaweed, kelp, cod liver oil, vitamins and mineral supplements) contain iodine. If the label lists iodine, do not take the supplement while on this diet.
- The best way to ensure a lower iodine content in your food is to prepare it from fresh ingredients. Table salt and sea salt with no added iodine may be used. Iodine is rarely added to salt in the UK.

This diet is based on iodine content of foods in the UK. Unlike some other countries YOU DO NOT NEED TO BAKE YOUR OWN BREAD OR DRINK DISTILLED WATER.

Please do not feel anxious about the diet. It is not necessary to limit yourself other than what has been listed. RAI was used successfully in the UK for many years before the diet was introduced.

Do I have to come into hospital for RAI treatment?

Yes, you will probably need to stay in hospital in the RAI or iodine suite for 2–4 days. How soon you go home depends on how quickly the radioactivity leaves your body.

There are different levels/doses. RAI patients who receive the lowest dose may only be in hospital for 24 h.

What happens on admission?

On the ward you will see members of the nursing, medical and nuclear medicine teams who will give an explanation of the treatment and details about the room where you will be staying. You will also have the opportunity to ask any questions that you might have.

You will be asked if there is any chance you could be pregnant. If there is any uncertainty then a pregnancy test will be performed to check that you are not pregnant before proceeding with the RAI treatment.

You will be asked to sign a form giving consent for the treatment if this has not already been done in clinic.

Who gives the capsule?

You will be given the RAI capsule by a member of staff from the nuclear medicine department. The capsule is about the size of a paracetamol capsule. Occasionally the treatment may be given as a liquid (which is colourless and tasteless).

What happens next?

You should not eat or drink anything for 2 h after talking the capsule to allow time for the iodine to be absorbed. After this time you should eat as normal and drink plenty of fluids.

Are there any visiting restrictions?

As the treatment is radioactive, people under the age of eighteen or pregnant women will not be allowed to visit you. Others may visit for a short time. The specific restrictions may vary. Staff will advise on a daily basis what length of visiting time is allowed.

Staff will spend only short periods of time in your room. When they bring in your meals and drinks they may stand behind a screen or in the doorway. You should try to maintain a safe distance of about 3 m. Staff won't stay and chat for long periods of time but do not hesitate to contact them if you need anything.

What happens at meal times?

The nursing or catering staff will bring meals to 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 thrown away in a bin provided. If there is any unwanted food this needs to be sealed in a plastic bag and put in the bin. Sometimes 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 may receive a menu to fill in for the next day although this will vary from centre to centre. Hot drinks are usually provided in the morning, mid-morning, lunch time, tea time and night-time. Some units have a fridge where you can store food and drink and/or a small kitchen where you can make your own hot drinks.

What about washing and hygiene?

As you should be drinking more than usual, you should also be using the toilet frequently. All your body fluids are radioactive and you must flush the toilet twice after each use. If you spill or splash urine, please contact the nursing staff. Your sweat is also radioactive, so we advise you take shower daily.

What can I bring in with me to help me relax or pass the time?

- You may take in a mobile phone. Most centres recommend that you take an old phone or a cheap replacement and just exchange the sim card. The phone is often placed in a plastic bag to reduce the direct contact with your hands.
- You may be able to bring DVDs, CDs and books with you; they may need to be monitored for radiation before they can be removed from your room.
- If any items are significantly radioactive they will need to be stored in the hospital for some time after you go home.
- Check with your specialist team regarding the use of laptop and tablet computers. Some centres will provide a lap top.
- If you need earphones, buy a cheap set that can be left behind.

Take travel size toiletries with you and leave your toothbrush behind when you leave.

The usual recommendation is to take your clothes home and wash them once on their own in your washing machine. There is no need to discard your clothes.

Please check your centre's specific recommendations beforehand as these may vary.

When can I go home?

The staff from the nuclear medicine or medical physics department will come to the ward to take radiation measurements each day. They can then work out how much radiation is still in your body and if the level is safe for you to go home. You must stay in your own room until that time.

You will have a whole body scan either on the day you are discharged home or during the first week following the treatment, in which case you will be asked to return to the hospital.

Will I still have any restrictions when I get home?

When you go home you should avoid close contact with babies, young children and pregnant women.

You will also need to limit close and prolonged contact with other people, and stay away from crowded places such as cinemas, theatres, public transport where you may be close to the same person for a prolonged period of time.

The nuclear medicine staff will explain to you how many days you need to limit yourself. This advice varies from patient to patient, is dependant on the dose of RAI who have received and differs for contact with adults and young children.

Medical or nursing staff will organise a new supply of thyroid tablets. If you stopped these during RAI you should restart these on the day you go home.

Will I have to come back to the hospital?

You will need to be seen again in the outpatient department by a member of the thyroid cancer care team. 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.

How will I be followed up?

You will be followed by the thyroid cancer care team and or your surgeon/endocrinologist at regular intervals to see how you are feeling and check your thyroid hormone levels.

If you are struggling and need emotional support, do let them know, or contact one of the patient support groups listed below.

Another important aspect of thyroid cancer treatment is thyroid stimulating hormone (TSH) suppression.

Your thyroid team will want to keep your thyroid hormone levels at a slightly higher level than would normally be required, by doing this the TSH will be 'turned off' or suppressed.

This will be required for at least the several months following diagnosis and for some patients it may be longer.

It is very important than no one other than your thyroid team such as your GP alters your thyroxine dose. Should this happen please refer them to your thyroid team before making any changes to your medication.

Some centres give out TSH alert cards for patients to carry.

About six to twelve months after RAI you will be called back for a scan (usually a neck ultrasound scan) and a thyroglobulin (Tg) blood test to see if the RAI has been successful. Tg is an important 'marker' for thyroid cancer and you will have ongoing Tg blood tests during the long term follow up period to check for any early signs of recurrence.

Most centres do a 'stimulated thyroglobulin test'. Before the blood test you will be given Thyrogen™ injections to raise the TSH level and asked to follow the low iodine diet. Alternatively you may be asked to stop your thyroid hormone treatment for 2 weeks prior to the blood test.

Will I need RAI treatment again?

Some people need additional RAI doses or surgery to make sure all the remaining thyroid tissue has been destroyed. This does not mean they are not going to be cured. Thyroid cancer is highly treatable and is cured in around 96% of cases. There are people alive now who were diagnosed more than 50 years ago.

Your centre may give you an information leaflet which has more details on how RAI is given in your local centre. Treatment details vary from place to place. Please contact your thyroid cancer care team if you have any questions or concerns after reading this information.

Patient support

Being diagnosed with a rare cancer can make you feel isolated.

You should be introduced to a Clinical Nurse Specialist (CNS) or a named Key Worker either at or shortly after your diagnosis. They are there to help you with any questions or worries you may have.

Talking to others who have been through it can help. Support and information are available through the patient-led organisations mentioned below who have collaborated in writing this leaflet. Together we can give you informational and emotional support to help you through your investigations, treatment and recovery.

Butterfly Thyroid Cancer Trust. Butterfly Thyroid Cancer Trust is the first registered charity in the UK dedicated solely to the support of people affected by thyroid cancer.

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

Thyroid Cancer Support Group – Wales. Supporting thyroid cancer patients and families not only in Wales but nationally and occasionally internationally. The group is funding the first national tissue bank specifically for research into anaplastic thyroid cancer.

Address: 'Morcote', Sunlea Crescent, New Inn, Pontypool, Gwent, South Wales NP4 8AD
Tel: 0845 009 2737
Website: www.thyroidsupportwales.co.uk
Email: thyroidgroup@tiscali.co.uk

British Thyroid Foundation. The British Thyroid Foundation is a charity dedicated to supporting people with all thyroid disorders and helping their families and people around them to understand the condition.

Address: 2nd Floor, 3 Devonshire Place, Harrogate, West Yorkshire GH1 4AA
Tel: 01423 709707/709448
Website: www.btf-thyroid.org
Email: info@btf-thyroid.org

Hypopara UK. Hypopara UK is the national patient organisation for people with parathyroid conditions, including post-surgical calcium issues and permanent hypoparathyroidism.

Address: 6 The Meads, East Grinstead, West Sussex RH19 4DF
Tel: 01342 316315
Website: www.hypopara.org.uk
Email: info@hypopara.org.uk

Association for Multiple Endocrine Neoplasia Disorders – AMEND. AMEND provides information and support to families with multiple endocrine neoplasia (MEN) and associated endocrine tumours, including medullary thyroid cancer.

The Warehouse, Draper Street, Tunbridge Wells, Kent TN4 0PG
Tel: 01892 516076
Website: www.amend.org.uk
Email: info@amend.org.uk

RAI is not used in the case of medullary thyroid cancer as it is not effective in this type of cancer.

Patient Information Leaflet 5: Medullary thyroid cancer

What is medullary thyroid cancer?

Medullary thyroid cancer (MTC) is a rare form of cancer of the thyroid gland. It usually occurs as an isolated case on its own (sporadic), but it is sometimes inherited (i.e. passed down from one generation to the next in a family). One in four cases of MTC occurs as part of a rare inherited disorder called Multiple Endocrine Neoplasia Type 2 (MEN2). All patients diagnosed with MTC are offered a DNA test for MEN2.

The thyroid is situated at the front of the neck. This gland produces three hormones: thyroxine and triiodothyronine (essential for maintaining the body's metabolism and mental and physical development); and calcitonin (which has no known action in healthy people).

For more information see the British Thyroid Association Patient Leaflet – The Thyroid Gland

MTC originates from the parafollicular cells (C cells) of the thyroid, which produce calcitonin. Calcitonin can be measured in the blood of patients with MTC and this is used by doctors to keep a check on the disease MTC usually develops over a number of years but it can spread early on to nearby lymph nodes. If the cancer is still contained within the thyroid you may have an operation to remove the thyroid gland (called a total thyroidectomy) and some of the lymph nodes in the neck (called a lymph node dissection) and need no further treatment. If the calcitonin level is still raised after surgery, this can mean that the cancer has spread (i.e. it has become metastatic) or it has not been completely removed, and you may need more surgery and treatments to control it.

There is not yet a definitive cure for *metastatic* MTC. However, it is often slow growing and can be managed effectively and without symptoms for many years. Symptoms that may develop can sometimes be controlled by the use of radiotherapy and/or chemotherapy.

There are new anticancer drugs called tyrosine kinase inhibitors TKIs), which are becoming available for the treatment of various types of cancers, including metastatic MTC. However, their effectiveness in prolonging life is not yet known.

How is MTC diagnosed?

You may notice a lump in the neck, which was not there before, or this may be noticed by a partner or colleague. Sometimes the raised calcitonin level may cause diarrhoea, and it is not immediately apparent that this may be associated with a problem in the neck. A diagnosis of MTC may be confirmed by a fine needle biopsy, and ultimately by surgery. A blood test to measure calcitonin can sometimes be used to make the diagnosis of MTC, but levels may be raised for a variety of other reasons, and so most specialists prefer not to use it for diagnosing MTC.

Can children have MTC?

It is rare for children to be diagnosed with MTC. Children who are diagnosed with MTC but who have no known family history of MTC should be seen by a genetics specialist to check whether they have MEN2 (an inheritable genetic disorder). If they have this condition they will need screening for other potential MEN2-related problems. A referral to a genetic counsellor at your Regional Genetics Service Centre should be made by your specialist or GP if appropriate.

What tests will I have for MTC?

You may have the following tests to confirm a diagnosis of MTC:

Blood tests: baseline calcitonin. This is a simple blood test to measure calcitonin levels, which are usually raised when MTC is present (note that once drawn, the blood must be taken immediately and on ice to a chilled centrifuge in the lab). However, it is not as reliable as other tests and is rarely used for diagnosing MTC in the UK.

Fine needle aspiration (FNA). This is done in a hospital outpatient clinic. A very thin needle is inserted into any swelling you may have in your neck and a sample of cells is taken out. These cells are then analysed under a microscope. This is a very reliable way of diagnosing MTC.

Thyroid ultrasound scan. A picture of the thyroid gland is obtained by using sound waves which will show any solid lumps or cysts. This cannot diagnose cancer on its own but it can help with the overall diagnosis and in planning treatment.

How is MTC treated?

MTC is different from other types of thyroid cancer. It is best treated in a hospital that is a centre of expertise for MTC, and by an experienced endocrine or head-and-neck surgeon who regularly operates on such patients.

Once a diagnosis of MTC has been made, you will have an ultrasound scan of your neck and sometimes a CT scan to try to determine how advanced the disease is. If there appear to be no enlarged lymph nodes, surgery to remove the thyroid and nearby lymph nodes (total thyroidectomy and central node dissection) is performed. If enlarged or involved lymph nodes are found, other lymph nodes will be removed at the same time.

If MTC is diagnosed before surgery, special blood and urine tests should be done (even if there is no family history of MEN2) to rule out the presence of a phaeochromocytoma (adrenal gland growth) and overactivity of the parathyroid glands.

What will my scar look like?

During total thyroidectomy and central node dissection, a small incision is made at the base of the front of the neck through which the thyroid and nearby lymph nodes can be removed. A larger incision is required if the removal of other neck lymph nodes is necessary. Eating and drinking is possible almost immediately after waking from the operation.

How long will I stay in hospital?

You will usually stay in hospital for between 2 and 4 days depending on the extent of your operation.

What are the risks of the operation?

Thyroid surgery is generally safe but there are some possible risks you need to be aware of.

There is a risk of bleeding or infection in the days and weeks after the operation. There is also a risk of temporary voice change due to nerve injury, which in a few cases may become permanent (see below). Despite the surgeon's best efforts some people will have an unsightly neck scar (see below).

There is also a risk of injury to the parathyroid glands. This may be temporary or permanent and can affect the level of calcium in the body (see below).

Sometimes the lymph node removal is done along the side of the neck towards the ear on one or both sides. During this procedure there may be injury to the 'accessory nerve' (an important nerve in the neck which helps you to turn your head and shrug your shoulders) which may require physiotherapy.

Will it affect my voice?

The thyroid gland lies close to the voice box (larynx) and the nerves to the voice box. If you depend on your voice in your work or hobbies you should discuss this with your surgeon.

Before the operation you should have a vocal cord check. This involves spraying some local anaesthetic into your nose to make the procedure as painless as possible. A thin flexible camera (endoscope) is then gently passed into one nostril and from there down into your throat.

After your surgery you may find that your voice sounds hoarse and weak, and your singing voice may be altered. Temporary voice change can occur in up to 10% of cases, but permanent injury is uncommon and happens in less than two percent of cases. If this happens, ask your surgeon about possible treatment such as speech therapy or further surgery.

Will it affect my calcium levels?

The thyroid gland lies close to four tiny parathyroid glands. These glands, each about the size of half a pea, produce parathyroid hormone (PTH) that regulates levels of calcium in your blood. They may be affected during a thyroidectomy and may stop producing as much hormone as before. This is known as hypoparathyroidism. In 20–30% of cases this is temporary. In 5–10% of cases this may be permanent.

Without enough parathyroid hormone, your blood calcium levels may fall. Low calcium (hypocalcaemia) may mean you feel generally unwell or cause symptoms such as tingling in your lips or fingers or cramps. Either way, you should tell a doctor or nurse immediately. You will be given a blood test and, if low calcium is confirmed, some calcium via a drip or as a tablet.

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

After the operation, you may feel some discomfort and stiffness around your neck but you will be given some medication to help ease this. Pain relief may be given as injections, liquid medicine or tablets. Most patients are up and walking around after the first day. After a few weeks your neck and shoulder movements should be back to normal.

If you have had more extensive neck surgery to remove some of your lymph nodes you may need to be referred to a physiotherapist.

For more information see the BTA Patient Leaflet – Thyroid Surgery

Will I need to take medication afterwards?

You will need to take levothyroxine tablets as prescribed by your doctor for the rest of your life. To make sure that you are on the correct dose, you will have regular blood tests to check that your thyroid hormone levels are within normal limits.

Doses are typically between 100 and 150 mcg a day for adults, lower for children.

Too high a dose of levothyroxine may cause symptoms such as rapid heartbeat, sweating, anxiety, tremor and loss of weight. Too low a dose may cause symptoms such as lethargy, slow heartbeat, sensitivity to cold, and weight gain. The same symptoms can also occur in other conditions, so you will need a blood test to measure the thyroid stimulating hormone (TSH) level to find out whether your levothyroxine dose needs to be changed. Once you are on a stable dose, as judged by blood tests, repeat tests usually only need to be done once a year in adults, or more frequently in children and teenagers as they grow.

If your parathyroid glands have been affected by surgery, you may need to take calcium carbonate supplements to maintain blood calcium levels until the parathyroid glands recover. A special type of vitamin D, such as Alfacalcidol or Calcitriol, in the form of capsules or drops, is used to help you absorb calcium from your diet if necessary. Treatment is usually temporary (up to 6 months).

If you begin to suffer from headaches, nausea and vomiting, this may mean that your calcium levels are too high and that the Alfacalcidol or Calcitriol is no longer needed. Too low a dose will lead to pins and needles or cramping in the hands or feet which may be temporary or may mean the dose needs to be increased. If you have symptoms you should see your doctor or nurse.

In some cases the parathyroid glands are permanently injured or removed during surgery and you will need to take calcium and vitamin D tablets for life. You should be referred to a consultant endocrinologist who will monitor your blood, bones and kidneys regularly and adjust your medication when necessary. Your GP will care for you between hospital appointments and will organise regular blood tests, particularly during medication adjustments. Once your levels are stable you should be able to lead a normal life.

What happens if the MTC has spread?

You may have high blood calcitonin levels even after complete surgical treatment. This indicates that there are MTC cells left in the body. However, patients with higher than normal calcitonin levels that remain the same over a period of time, or increase slowly, do not necessarily need further investigation or treatment. This is because calcitonin alone is not an indication of a growing tumour and scans are unlikely to identify a site of disease outside of the neck unless calcitonin levels are significantly high.

In some patients, however, the search for cancer that has spread (metastatic disease) may involve further tests. These may include ultrasound of the neck, CT scan, radioactive isotope scans or other types of scan. This may be followed by treatment with more surgery, radiotherapy or other radiation treatments (MIBG/Octreotide).

There are new anticancer drugs called Tyrosine Kinase Inhibitors (TKIs) which are becoming available for the targeted treatment of various types of cancers, including metastatic MTC. One of these, vandetanib, has been approved for use in the treatment of metastatic MTC in the UK. These drugs can cause significant side effects. Other TKIs are currently only available in clinical trials.

What are MIBG and octreotide therapies?

Where surgery is no longer an option, some specialised medical centres may use radiolabelled octreotide or MIBG (Meta-Iodo-Benzyl-Guanidine) radioactive therapies to help reduce or control the spread. However, these are only appropriate if tests suggest that the radioisotope will be taken up by the tumour. The agent is attached to a radioactive substance, and is given through a vein by slow injection. You will remain radioactive for a few days and will need to be nursed in a lead-lined room. The treatment may need to be repeated several times at 3 or 6 month intervals. There are few side effects to this therapy but you may experience some nausea, and occasionally vomiting. Patients usually tolerate these side effects well.

Until a complete cure is found, much of the current focus of treatment for extensive metastatic MTC is on the relief of the symptoms it causes:

Diarrhoea. You may need to adjust your diet and take an anti-diarrhoea medication such as Imodium, which contains loperamide. Some of the tumours contain somatostatin receptors, and in these instances treatment with a long-acting form of somatostatin (octreotide or lanreotide) may sometimes be helpful.

Flushes. Anti-ulcer medications called histamine receptor blockers (H_2 blockers such as cimetidine or ranitidine) may occasionally be prescribed to help ease flushing.

Pain. Painful bone metastases may be suitable for external radiation therapy, which can provide rapid relief. In all cases, pain medications may be prescribed.

Where can I get other help?

Free Prescriptions. Currently, patients in Scotland, Wales and Northern Ireland do not have to pay for their prescriptions. Patients in England taking lifelong levothyroxine or who are diagnosed with hypoparathyroidism are currently entitled to free prescriptions for all medicines. You should obtain the appropriate leaflet from your doctor who will sign it and send it on. You will then receive an exemption certificate, which you must show to your pharmacist when collecting medicines.

MedicAlert®. Anyone taking life-long medications should consider getting and wearing a MedicAlert® identification emblem. This contains summarised information of your medical condition and a 24-h Helpline number which emergency medical staff can call to get detailed information about your medical condition from the MedicAlert database.

This leaflet was adapted from the Association for Multiple Endocrine Neoplasia Disorders – AMEND – information resources by Jo Grey.

Patient support organisations

The following patient-led organisations collaborated in the preparation of this leaflet and each provides information and support and the chance to speak to other patients who have been through surgery and treatment for thyroid cancer.

Association for Multiple Endocrine Neoplasia Disorders – AMEND. AMEND provides information and support to families with multiple endocrine neoplasia (MEN) and associated endocrine tumours, including medullary thyroid cancer (MTC).

Address: The Warehouse, Draper Street, Tunbridge Wells, Kent TN4 0PG
Tel: 01892 516076
Website: www.amend.org.uk
Email: info@amend.org.uk

British Thyroid Foundation. The British Thyroid Foundation is a charity dedicated to supporting people with all thyroid disorders and helping their families and people around them to understand the condition.

Address: 2nd Floor, 3 Devonshire Place, Harrogate, West Yorkshire GH1 4AA
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Hypopara UK. Hypopara UK is the national patient organisation for people with parathyroid conditions, including post-surgical calcium issues and permanent hypoparathyroidism.

Address: 6 The Meads, East Grinstead, West Sussex RH19 4DF
Tel: 01342 316315
Website: www.hypopara.org.uk
Email: info@hypopara.org.uk

Thyroid Cancer Support Group – Wales. Supporting thyroid cancer patients and families not only in Wales but nationally and occasionally internationally. The group is funding the first national tissue bank specifically for research into anaplastic thyroid cancer.

Address: 'Morcote', Sunlea Crescent, New Inn, Pontypool, Gwent, South Wales NP4 8AD
Tel: 0845 009 2737
Website: www.thyroidsupportwales.co.uk
Email: thyroidgroup@tiscali.co.uk

British Thyroid Association Patient Information Leaflet 6: Advanced or higher risk differentiated (papillary and follicular) thyroid cancer

Many patient information leaflets focus on the diagnosis and treatment of early stage differentiated thyroid cancer. This can be frustrating when you are facing something more complex.

This leaflet aims to explain some investigations and treatments that patients with more advanced or high risk thyroid cancer may need to undergo. It is not possible to mention every situation but the most common ones are explained below.

Hearing that your thyroid cancer is more complex is daunting. Unlike many more common cancers, however, it is often possible to live for longer with advanced or higher risk thyroid cancer and enjoy a good quality of life.

What does advanced or higher risk thyroid cancer mean?

This term is used when referring to patients who need more than neck surgery and one dose of radioactive iodine (RAI) treatment in order to eliminate all traces of thyroid cancer.

This still covers a wide range of situations ranging from someone who may be given a series of RAI treatments to get rid of their cancer completely to someone who may have thyroid cancer that has spread to other parts of the body and who no longer benefits from RAI treatment.

What makes my cancer advanced or high risk?

The risk category that you fall into will depend on factors such as your age, gender, and features related to your particular thyroid cancer. These include tumour size, whether the cancer has extended beyond the thyroid gland; whether the cancer has spread to other parts of the body; whether it is possible to remove the bulk of the cancer by thyroid surgery; and whether the initial RAI treatment has been successful.

The following sections cover a number of different situations that can arise. Not all of them may be relevant to you.

I have had a thyroidectomy and RAI and have been told my follow up thyroglobulin (Tg) blood test has not returned to normal. What does this mean?

If you still have thyroglobulin detectable in your blood this means there are still thyroid cells (either normal or cancer cells) present somewhere in your body. Sometimes in this situation a neck or body scan will not show where the thyroid cells are in the body. This is more likely when the level of thyroglobulin is not very high.

What happens next will depend on your particular circumstances. Your doctor will take into account how close to normal your thyroglobulin result is and the features of your particular thyroid cancer when deciding what to do.

If your thyroglobulin test result is close to normal, you may be advised to have a repeat thyroglobulin blood test after perhaps 6–12 months. Alternatively you may be advised to undergo another RAI treatment. It is not uncommon for patients to need more than one RAI treatment to remove all traces of thyroid tissue (whether that is normal or cancer containing thyroid tissue).

I have had a thyroidectomy and RAI treatment and been told my follow up scan is not normal, what does this mean?

If your follow-up ultrasound scan of the neck has shown enlarged or odd looking lymph glands you may need to have more tests including a biopsy, and you may be referred back to your thyroid surgeon to consider whether the lymph glands can and should be removed. This will depend on where the glands are in your neck, how big they are, how well you are and obviously your wishes.

If surgery is not performed then you will be advised on whether you need RAI treatment or possibly radiotherapy (x ray) treatment instead (described in more detail below).

I have been told that I need radiotherapy to my neck. What does this involve?

Radiotherapy involves using powerful x-ray beams to try and kill cancer cells whilst allowing the normal cells around the same area to survive.

The treatment is given in a radiotherapy department and the machines are called linear accelerators or Linacs.

Treatment is usually given over a period of several weeks on a Monday to Friday basis (no treatment at the weekends usually). You may be in the treatment room for a total of about 20 min each day.

It is important to keep the position of your head and neck as still as possible during treatment so a special plastic mask is usually made that fits snugly around the shape of your face and neck. There are different types of mask. You only wear the mask whilst you are on the treatment bed.

You are treated lying on your back. You do not feel anything whilst the *x* ray beam is switched on but you can usually hear the machine working.

The treatment is likely to cause some side effects. The commonest ones are:

- painful swallowing
- dry mouth
- dry, red, painful or blistered skin in the region of the treatment
- altered sense of taste
- tiredness
- (feeling sick/nausea and hair loss are not likely to occur)

The side effects will vary depending on exactly what part of the body needs treating and your doctor will explain in detail the likely effects that you might experience and whether they are likely to be temporary or longer lasting.

I am on follow-up and have been told my thyroglobulin blood test result is higher than normal and rising. What does this mean?

Thyroglobulin is only made by normal thyroid cells and differentiated thyroid cancer cells. If you have had your thyroid gland removed and you have received RAI you shouldn't have any normal thyroid cells left, so a raised thyroglobulin level is likely to be due to some remaining thyroid cancer cells. If your thyroglobulin was previously normal, your doctor will discuss with you how best to investigate what is going on.

How is a raised thyroglobulin blood test result investigated?

There are a number of different tests. Not all of them may be relevant to your situation and your doctor will explain what is needed.

Tests include:

- Neck ultrasound scan: this can assess where your thyroid gland used to sit (called the thyroid bed) as well as the lymph gland areas of the neck. It may be combined with a needle biopsy if the scan shows something abnormal
- Computerised tomography (CT) scan of chest: this assesses the lymph nodes in the central area in the chest (called the mediastinum) as well as the lungs
- CT or Magnetic Resonance Imaging (MRI) scan of other parts of the body depending on symptoms and results of other tests
- Isotope bone scan: this involves an injection of a small amount of a radioactive chemical into the bloodstream followed by a scan of the entire skeleton. The radioactive chemical can show areas of bone that are either more active or less active than normal. The results are sometimes difficult to interpret however as arthritis or old fractures can also show up. In these cases your doctor may recommend another type of scan to gather some more information
- Positron Emission Tomography (PET)-CT scan: this is used less often and is another form of radioactive scan that involves an injection along with a scan of the whole body

I have a raised thyroglobulin blood test but my scans have not shown where my cancer is

This may seem a bit confusing or worrying for you but is a fairly common situation. Your thyroid cancer doctor will have come across this situation a lot of times.

The usual reason for this situation to arise is that very small lesions cannot be seen or may be hidden.

It is common for the thyroglobulin level to rise first before anything can be seen on a scan. Thyroglobulin tests are very sensitive and can detect signs of remaining thyroid cells (normal or cancer containing) or recurring thyroid cancer cells before they become visible on scans.

In this situation your specialist may consider a trial of RAI treatment to see if the whole body RAI scan after treatment shows where the disease is and to see if your thyroglobulin result improves afterwards. This is sometimes called 'empiric' RAI treatment.

Your doctor will discuss the available options with you. This may include simply monitoring the thyroglobulin.

I have a raised thyroglobulin blood test result and scans have shown my cancer has spread to my lungs

Usually there are lots of small areas of thyroid cancer in both lungs rather than one larger lump and because of this surgery and radiotherapy are not usually the right options.

The most likely treatment option to be discussed with you in this situation is RAI treatment. The final decision will however take into account any other medical conditions you may have, how well you feel, and any previous treatments you have received. The possible benefits of treatments along with any side effects will be discussed so that you are able to make a decision that suits you.

I have a raised thyroglobulin blood test result and scans have shown my cancer has spread to my bones

If your scans have shown just one area of bone affected by thyroid cancer your doctor may suggest asking an orthopaedic or spinal surgeon to review your scans to see if surgery may be helpful. Surgery is not always possible however. It will depend on which bone(s) is affected, what the surgery would entail and any other medical conditions you may have.

Radiotherapy (x-ray) treatment is sometimes recommended after surgery or instead of surgery. The number of radiotherapy treatments you are offered depends on a number of factors. One or five daily outpatient treatments are commonly used.

Your doctor will want to know if the bone disease is causing you any problems with pain or with your daily activities and will discuss pain medication and possibly bone strengthening medicine (e.g. bisphosphonates) with you.

I have a raised thyroglobulin blood test result and scans have shown my cancer has spread to lots of different places in my body

Your doctor will need to find out if you are experiencing any symptoms from the areas of cancer shown up on the scans and advise you on how these are best treated. The symptoms will depend on where the areas of cancer are in the body and may include shortness of breath or bone pain.

Thyroid cancer that has spread from the thyroid gland to other parts of the body is called metastatic cancer. These areas are often called 'secondaries'.

It is not always possible to get rid of thyroid cancer once it has spread in this way so the treatment is aimed at trying to reduce the amount of cancer that is present, to improve symptoms, to try and keep people as independent as possible, and to maintain quality of life. It is often possible to live for longer with thyroid cancer secondaries with a good quality of life compared with other cancers you may have heard of.

The first treatment type that is considered in this situation is RAI. This will depend on a number of factors including whether you have had benefit from any previous RAI treatments as well as taking into consideration any other medical conditions you may have and how well you feel. RAI treatment isn't always appropriate.

Chemotherapy (drug treatment) is used in the treatment of many types of cancer but isn't commonly used for thyroid cancer patients. If your doctor feels you might benefit however, they will talk to you about what this would involve and what potential benefits you may gain. The drugs most commonly used in this situation include doxorubicin or epirubicin or a combination of doxorubicin and cisplatin.

I have been told that RAI treatment is no longer working for me

This is a relatively common situation and is often called non RAI avid disease or RAI refractory disease. This occurs when thyroid cancer cells lose their ability to take up RAI and therefore the radiation energy cannot kill off the cancer cells. If this has happened you won't get any benefit from further RAI treatment.

There are new anticancer drugs called 'tyrosine kinase inhibitors' (TKIs) which are becoming available for the targeted treatment of various types of cancers. There are currently no licensed targeted therapies for use in thyroid cancer but this is expected to change. Examples include sorafenib and lenvantinib.

Your doctor will talk to you about any available clinical trials that may be suitable for your situation. These aren't always available in every cancer hospital so if there is a trial available it may involve referring you to another hospital for further discussion.

Patient support

Being diagnosed with a rare cancer can make you feel isolated. Talking to others who have been through it can help. Support and information are available through the patient-led organisations mentioned below who have collaborated in writing this leaflet. Together we can give you informational and emotional support to help you through your investigations, treatment and recovery.

Butterfly Thyroid Cancer Trust. Butterfly Thyroid Cancer Trust is the first registered charity in the UK dedicated solely to the support of people affected by thyroid cancer.

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

Thyroid Cancer Support Group – Wales. Supporting thyroid cancer patients and families not only in Wales but nationally and occasionally internationally. The group is funding the first national tissue bank specifically for research into anaplastic thyroid cancer.

Address: 'Morcote', Sunlea Crescent, New Inn, Pontypool, Gwent, South Wales NP4 8AD
Tel: 0845 009 2737
Website: www.thyroidsupportwales.co.uk
Email: thyroidgroup@tiscali.co.uk

British Thyroid Foundation. The British Thyroid Foundation is a charity dedicated to supporting people with all thyroid disorders and helping their families and people around them to understand the condition.

Address: 2nd Floor, 3 Devonshire Place, Harrogate, West Yorkshire GH1 4AA
Tel: 01423 709707/709448
Website: www.btf-thyroid.org
Email: info@btf-thyroid.org

Hypopara UK. Hypopara UK is the national patient organisation for people with parathyroid conditions, including post-surgical calcium issues and permanent hypoparathyroidism.
Address: 6 The Meads, East Grinstead, West Sussex RH19 4DF
Tel: 01342 316315
Website: www.hypopara.org.uk
Email: info@hypopara.org.uk

The following websites provide additional information:

- Types of scan:
  - www.goingfora.com.
- Radiotherapy:
  - http://www.macmillan.org.uk/Cancerinformation/Cancertreatment/Treatmenttypes/Radiotherapy/Radiotherapy.aspx.
  - www.goingfora.com/oncology/radiotherapy_room.html.
  - http://www.cancerresearchuk.org/cancer-help/about-cancer/treatment/radiotherapy/external/plan/radiotherapy-moulds#masks.

- Drug treatment:
  - http://www.macmillan.org.uk/Cancerinformation/Cancertreatment/Treatmenttypes/Chemotherapy/Individualdrugs/Individualdrugs.aspx.
- Clinical Trials:
  - http://www.macmillan.org.uk/Cancerinformation/Cancertreatment/Clinicaltrials/Clinicaltrials.aspx.

First issued February 2014.

British Thyroid Association Patient Information Leaflet 7: Anaplastic thyroid cancer

What is anaplastic thyroid cancer?

Anaplastic thyroid cancer is the rarest type of thyroid cancer. There are perhaps 70–90 patients diagnosed each year in the UK.

Anaplastic thyroid cancer is treated differently from other types of thyroid cancer. Information leaflets written for patients with these other types of thyroid cancer may therefore not be very helpful to you.

This leaflet has been written to provide general information on anaplastic thyroid cancer for patients, their family and friends. Not all of the information included in this leaflet will apply to your particular situation so it is important to remember there are lots of variations between people and their problems.

What symptoms can anaplastic thyroid cancer cause?

You may or may not experience some of the following symptoms:

- swollen neck
- pressure symptoms in the neck due to an enlarged thyroid gland pressing on the surrounding area. This can feel tight and uncomfortable
- swallowing difficulty. The thyroid gland sits close to the gullet and as it gets bigger it can cause pressure
- breathing difficulty because the cancer can affect the voice box
- noisy breathing
- altered voice including hoarseness or a weak voice
- shortness of breath and
- bone pain (this is uncommon)

How is anaplastic thyroid cancer diagnosed?

Tests will already have been done in order to make your diagnosis. Common tests include:

- Needle biopsy (fine needle aspiration or FNA)
- Core biopsy and
- Scans. This might include ultrasound, CT or MRI scans

A small number of people may already have had all or part of their thyroid gland removed.

Your test results will have been reviewed and the information put together to discover how big the thyroid cancer is and what parts of the body are affected. This will help when it comes to making decisions and choices on treatment.

What type of treatment might be suitable for me?

The decision about which treatment is best in your particular situation will be made jointly between you and your doctors.

The choice of treatment will depend on your general health and well-being as well as the results from your tests.

For some patients, the cancer may still be contained within their thyroid gland. In this case an operation to remove the thyroid gland and any surrounding cancerous tissue may be possible. This isn't always straightforward, however. Your doctors will explain the operation to you in more detail if they think it is suitable for you.

Patients who undergo a thyroid operation may also have other treatments suggested after the surgery is completed in order to increase the chances of controlling the cancer. This may involve x-ray treatment (radiotherapy) with or without drug treatment (chemotherapy).

If an operation with a general anaesthetic is not possible, due either to other health problems or to patient choice, it may be possible to offer a course of x-ray therapy (radiotherapy) with or without drug treatment (chemotherapy).

For many patients their tumour will be quite large and may have grown beyond the thyroid gland or spread to other parts of the body. This can make treatment decisions difficult. In this situation it will not be possible to remove the cancer with a thyroid gland operation or to try and control the cancer using high dose x-ray therapy. In this situation the emphasis of treatment will be to try and improve any symptoms and to maintain independence and quality of life. This is what we call supportive treatment or palliative treatment.

Some patients may, for example, need help with:

- softer foods or liquid food supplements if swallowing is difficult
- painkillers if they have neck discomfort
- inhalers, nebulisers or oxygen if they have shortness of breath
- very occasionally, a breathing tube (tracheostomy) may be considered in order to help someone breathe more easily and
- steroids are sometimes used to help with breathing or to reduce swelling around a tumour area

As this is a rare disease, it has been difficult to research and to introduce new treatments into routine medical practice. Thyroid cancer specialists are, however, very keen to offer patients the opportunity to take part in clinical trials whenever there is a suitable project or trial available. Your medical team can talk to you about any available options.

The future

Cancer patients and their loved ones face many uncertainties about the disease, its treatment and the future. Seeking information about the future is a very personal decision. For patients with anaplastic thyroid cancer this can be particularly difficult decision due to the aggressive nature of the disease.

Many people with cancer want to know their prognosis, i.e., will they survive this illness. Some people find it easier to cope when they know the likely course of their disease; they may ask their doctor about their chance of survival or search for this information on their own. Other people find statistical information confusing and frightening, and think it is too impersonal to be of value to them. It is very important that each patient decides for themselves how much information he or she wants.

A doctor who is most familiar with your situation such as your cancer specialist is in the best position to discuss your prognosis and explain what the statistics may mean if this is what you decide.

You may have been told that anaplastic thyroid cancer is an aggressive form of thyroid cancer and that it is not possible to cure the majority of patients. While no one can predict for certain what will happen to you as an individual, your doctors will have some useful information from your tests and this will help make the right treatment decisions for you.

Even for patients with smaller anaplastic thyroid cancers that are confined to the neck area it isn't possible to guarantee a successful result after treatment. All patients therefore need close monitoring to check how well they are and to address any problems that may arise. Whatever treatment decisions are made, you will continue to have support and advice from people experienced in the treatment of this disease.

Who can help?

Coping with anaplastic thyroid cancer is difficult. You may need time to think about the changes that have happened. It can affect many areas of your life such as your emotions, relationships, finances and work. But you do not have to face your treatment on your own. There are many people available to help you and your family:

- your cancer specialist doctor (oncologist) or specialist cancer nurse;
- your GP and district nurses;
- a social worker;
- the Palliative Care Team – this is a team of doctors, nurses, therapists and others who work in hospitals and can visit you at home. They are experienced in assessing and treating symptoms and can offer support to you and your family; and
- thyroid cancer patient support organisations (see below).

This leaflet was written by Dr Laura Moss.

Patient support

The following patient-led organisations collaborated in the preparation of this leaflet and each provides information and support and the chance to speak to other patients who have been through surgery and treatment for thyroid cancer.

Butterfly Thyroid Cancer Trust. Butterfly Thyroid Cancer Trust is the first registered charity in the UK dedicated solely to the support of people affected by thyroid cancer.

Address: PO Box 205, Rowlands Gill, Tyne & Wear NE39 2WX
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Address: 'Morcote', Sunlea Crescent, New Inn, Pontypool, Gwent, South Wales NP4 8AD
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