ISBN 0-9551487-0-7

The United Kingdom Children's Cancer Study Group

British Society of Paediatric Endocrinology & Diabetes

Paediatric Endocrine Tumours

A Multi-Disciplinary Consensus Statement of Best Practice from a Working Group Convened Under the Auspices of the BSPED and UKCCSG (rare tumour working groups)

Endorsed by the Clinical Committee of the Society for Endocrinology (SfE)

Edited by

Helen A Spoudeas

In conjunction with invited representatives from the:

British Association of Endocrine Surgeons (BAES)
British Association of Paediatric Surgeons (BAPS)
British Society of Human Genetics (BSHG)
British Paediatric Neurosurgical Group (BPNG)
Radiotherapy, Radiology and CNS Tumour Divisions of UKCCSG

October 2005

The United Kingdom Children's Cancer Study Group

British Society of Paediatric Endocrinology & Diabetes

The United Kingdom Children's Cancer Study Group

British Society of Paediatric Endocrinology & Diabetes

Paediatric Endocrine Tumours

A Multi-Disciplinary Consensus Statement of Best Practice from a Working Group Convened Under the Auspices of the BSPED and UKCCSG (rare tumour working groups)

Endorsed by the Clinical Committee of the Society for Endocrinology (SfE)

Editor

Helen A Spoudeas

Assistant Editor

Barney Harrison

In conjunction with invited representatives from the:

British Association of Endocrine Surgeons (BAES)
British Association of Paediatric Surgeons (BAPS)
British Society of Human Genetics (BSHG)
British Paediatric Neurosurgical Group (BPNG)
Radiotherapy, Radiology and CNS Tumour Divisions of UKCCSG

October 2005

Acknowledgements

Grateful thanks are expressed to the many independent reviewers of these guidelines who devoted much time and care to considering the document and whose recommendations and suggestions for improvements were most valuable. They included hospital consultant physicians and surgeons expert in thyroid cancer, multiple endocrine neoplasia, pituitary and adrenal tumours, neuro-endocrinology and cancer genetics.

Thanks are also due to the members of the consensus development group and invited specialist consultants for their expert contributions, and to Novo Nordisk Ltd who provided financial support for this endeavour but did not seek, nor offer any editorial influence on the recommendations.

ISBN 0-9551487-0-7

The British Society of Paediatric Endocrinology and Diabetes (BSPED)
http://www.bsped.org.uk

UK Children's Cancer Study Group (UKCCSG)
http://www.ukccsg.org
University of Leicester, 3rd Floor, Hearts of Oak House, 9 Princess Road West, Leicester LE1 6 TH.
Registered Charity No: 286669

Published by Novo Nordisk Ltd, Broadfield Park, Brighton Road, Crawley,
West Sussex RH11 9RT United Kingdom

Contents

Consensus Development Group

Members of the Rare Endocrine Tumour Group

Chaired by Helen A Spoudeas,
Consultant Paediatric Endocrinologist,
London Centre for Paediatric Endocrinology,
University College and Great Ormond Street Hospitals, London.

Membership formed from consultant representatives of :
BSPED - Endocrine Tumour Group
Chair: Helen Spoudeas
UKCCSG - Rare Tumour Group
Chairs: David Walker,(past) Professor of Paediatric Oncology, Nottingham
Bernadette Brennan,(current) Consultant Paediatric Oncologist, Manchester

Working Party Members and Contributors to Each Guideline

Tumour considered			Professional body represented
<u>Craniopharyngioma</u>			
Guideline Working Group Members			
Lead	Dr Helen Spoudeas	Paediatric Endocrinologist, London	BSPED, UKCCSG
	Dr Assunta Albanese	Paediatric Endocrinologist, London	BSPED
	Dr Frank Saran	Clinical Oncologist, London	UKCCSG
	Dr Catherine De Vile	Paediatric Neurologist, London	BPNA, BSPED
	Mr Conor Mallucci	Paediatric Neurosurgeon, Liverpool	BPNG, UKCCSG
Consultation Advisors	Mr Ken Nischal	Paediatric Ophthalmologist,London	RCS (Faculty of Ophthalmology)
	Dr Kling Chung	Neuroradiologist, London	UKCCSG, RCR
	Mr Richard Hayward	Paediatric Neurosurgeon, London	BPNG
	Mr Mike Powell	Pituitary Neurosurgeon, London	RCS (Faculty of Neurosurgeons)
	Dr Barry Pizer	Paediatric Oncologist, Liverpool	UKCCSG (Chair CNS Tumour Division)
	Dr Richard Stanhope	Paediatric Endocrinologist, London	BSPED
	Dr Mark Gaze	Clinical Oncologist, London	UKCCSG (Chair Radiotherapy Division)
	Ms Alex Owen	Senior Staff Nurse, Paediatric Neurosurgery, London	RSCN

Adrenocortical Tumours

Guideline Working Group Members

Lead	Prof Richard Grundy	Paediatric Oncologist, Nottingham	UKCCSG
	Dr John Honour	Consultant Clinical Scientist, London	BSPED
	Prof David Walker	Paediatric Oncologist, Nottingham	UKCCSG
	Dr Hamish Wallace	Paediatric Oncologist, Edinburgh	UKCCSG, BSPED
	Prof Peter Hindmarsh	Paediatric Endocrinologist, London,	BSPED,
	Dr Vicky Murday	Cancer Geneticist, Glasgow	BSHG
	Mr Roly Squire	Paediatric Surgeon, Leeds	BAPS, UKCCSG, BAES
	Dr Bernadette Brennan	Paediatric Oncologist, Manchester	UKCCSG
	Mr Barney Harrison	Endocrine Surgeon, Sheffield	BAES
	Dr Charles Buchanan	Paediatric Endocrinologist, London	BSPED
	Dr Assunta Albanese	Paediatric Endocrinologist, London	BSPED
	Dr Helen Spoudeas	Paediatric Endocrinologist, London	BSPED, UKCCSG
Consultation Advisors	Mr Rob Wheeler	Paediatric Surgeon, Southampton	BAPS, UKCCSG
	Dr Charles Stiller	Epidemiologist, Leicester	UKCCSG
	Dr Kieran McHugh	Paediatric Radiologist, London	UKCCSG (Chair Radiology Division)

Differentiated Thyroid Cancer

Guideline Working Group Members

Lead	Mr Roly Squire	Paediatric Surgeon, Leeds	BAPS, UKCCSG, BAES
	Mr Barney Harrison	Endocrine Surgeon, Sheffield	BAES
	Dr Hamish Wallace	Paediatric Oncologist, Edinburgh	UKCCSG
	Prof David Walker	Paediatric Oncologist, Nottingham	UKCCSG
	Dr Liz Crowne	Paediatric Endocrinologist, Bristol	BSPED
	Dr Vicky Murday	Cancer Geneticist, Glasgow	BSHG
	Dr Charles Buchanan	Paediatric Endocrinologist, London	BSPED
	Dr Bernadette Brennan	Paediatric Oncologist, Manchester	UKCCSG
	Dr Helen Spoudeas	Paediatric Endocrinologist, London	BSPED, UKCCSG
Consultation Advisors	Dr Clive Harmer	Thyroid Clinical Oncologist, London	RCR (Faculty of Clinical Oncology)
	Dr Kieran McHugh	Paediatric Radiologist	London UKCCSG (Chair Radiology Division)

Phaeochromocytoma

Guideline Working Group Members

Lead	Dr Caroline Brain	Paediatric Endocrinologist, London	BSPED
	Mr Roly Squire	Paediatric Surgeon, Leeds	BAPS, UKCCSG,BAES
	Mr Barney Harrison	Endocrine Surgeon, Sheffield	BAES
	Dr Vicky Murday	Cancer Geneticist, Glasgow	BSHG
	Dr Liz Crowne	Paediatric Endocrinologist, Bristol	BSPED
	Prof Peter Hindmarsh	Paediatric Endocrinologist, London	BSPED
	Dr Bernadette Brennan	Paediatric Oncologist, Manchester	UKCCSG
	Dr Helen Spoudeas	Paediatric Endocrinologist, London	BSPED, UKCCSG
Consultation Advisors	Prof. Mike Dillon	Paediatric Nephrologist, London	RCPCH
	Dr Kieran McHugh	Paediatric Radiologist, London	UKCCSG (Chair Radiology Division)

MEN 2 and Medullary Thyroid Carcinoma

Guideline Working Group Members

Lead	Dr Vicky Murday	Cancer Geneticist, Glasgow	BSHG
	Dr Caroline Brain	Paediatric Endocrinologist, London	BSPED
	Dr Liz Crowne	Paediatric Endocrinologist , Bristol	BSPED
	Mr Barney Harrison	Endocrine Surgeon, Sheffield	BAES
	Mr Roly Squire	Paediatric Surgeon, Leeds	BPS, UKCCSG, AES
	Dr Charles Buchanan	Paediatric Endocrinologist, London	BSPED
	Dr Helen Spoudeas	Paediatric Endocrinologist, London	BSPED, UKCCSG,

MEN 1 (including Hyperparathyroidism and Pituitary Tumours)

Guideline Working Group Members

Lead	Dr Liz Crowne	Paediatric Endocrinologist, Bristol	BSPED
	Dr Caroline Brain	Paediatric Endocrinologist, London	BSPED
	Dr Vicky Murday	Cancer Geneticist, Glasgow	BSHG
	Mr Barney Harrison	Endocrine Surgeon, Sheffield	BAES
	Mr Roly Squire	Paediatric Surgeon, Leeds	BPS, UKCCSG, BAES
	Dr Charles Buchanan	Paediatric Endocrinologist, London	BSPED
	Prof Peter Hindmarsh	Paediatric Endocrinologist, London	BSPED
	Dr Helen Spoudeas	Paediatric Endocrinologist, London	BSPED, UKCCSG

Invited Specialist External Reviewers from whom comments were received

Whole Document

Ashley Grossman	Professor Adult Neuroendocrinology, London
John Wass	Professor Adult Neuroendocrinology, Oxford
Raj Thakker	Professor of Medicine, Oxford
Malcolm Wheeler	Professor of Endocrine Surgery, Cardiff
Eamonn Maher	Professor of Cancer Genetics, Birmingham

Members of the Clinical Committee of the Society for Endocrinology (SFE)

Specific Tumour Guidelines

Craniopharyngiomas

Ian Pople Paediatric Neurosurgeon

Guideline ratified by the membership of the BPNG March 2005

Guideline ratified by the CNS Tumour Division of the UKCCSG July 2005

Adrenocortical Tumours

Raul Ribeiro Paediatric Oncologist, St Jude's Hopsital, USA

Differentiated Thyroid Cancer and Medullary Thyroid Cancer

Jayne Franklyn Professor of Medicine and Adult Thyroid Specialist, Birmingham

Workshop Participants

Participants in the 6 core member workshops chaired by Helen Spoudeas:
Caroline Brain, Vicky Murday, Barney Harrison, Liz Crowne, Assunta Albanese, Roly Squire, John Honour, Charles Buchanan, Peter Hindmarsh

Participants in the 4 oncology/endocrinology UKCCSG/BSPED liaison meetings chaired by David Walker or Bernadette Brennan:
Helen Spoudeas, Charles Buchanan, Caroline Brain, Vicky Murday, Richard Grundy, Hamish Wallace.

Participants in the 4 craniopharyngioma workshops chaired by Helen Spoudeas:
Catherine De Vile, Frank Saran, Assunta Albanese, in discussion with Richard Hayward, Conor Mallucci, Barry Pizer.

Development and Purpose of Consensus Recommendations and a National Registry

Cancer affects 1 in 500 UK children under 15years of age and 1 in 284 youngsters by the age of 24 years (cumulative risk). These data constitute "moderate risk" disease according to Department of Health (DoH) guidelines.

The establishment of the United Kingdom Children's Cancer Study Group (UKCCSG) in 1977 has led to impressive advancements in treatment and cure through its national registration and randomised multi-centre collaborative studies.

The British Society for Paediatric Endocrinology and Diabetes (BSPED) is the representative body of British Paediatric Endocrinologists.

The incidence of childhood endocrine tumours is, however, so extremely rare, that there is no published randomised evidence to determine best practice. It is unlikely that sufficient expertise can be gained in such cases without centralising treatment in specific nominated centres, in addition to the need to collect incidence and outcome data systematically through a national registration system. The latter has been confounded to date by the difficult distinction between malignant and benign disease in certain endocrine tumours, the prophylactic surgical treatment of at risk individuals identified through genetic screening, and the multiplicity of presentations to a number of paediatric or adult medical and surgical disciplines.

In November 2001, a multidisciplinary working party of paediatric endocrinologists, oncologists and surgeons together with adult surgeons, oncologists and clinical geneticists with paediatric expertise, was convened under the joint auspices of the BSPED and UKCCSG. Their remit was to specifically consider the endocrine tumours of childhood and compile consensus statements intended to inform healthcare purchasers and providers of acceptable standards of care for these patient groups.

Process of Development and Use of the Consensus Recommendations

Between November 2001 and November 2002, recognised UK authorities with a national reputation for clinical research were invited to produce background papers on specific aspects of each topic, summarising the relevant available English language published evidence from peer-reviewed journals into a guideline. These drafts were then considered and developed by small nominated groups consisting of 4-6 individuals with different multi-speciality expertise according to a pre-determined structure and headings.

Because of the potential for bias in consensus development by small groups, background papers were circulated to members of the full combined society membership group [rare endocrine tumour groups of the UKCCSG and BSPED] before detailed consideration of each paper at a total of 6 core workshops held at the Royal College of Surgeons/Royal Society of Medicine and a further 4 endocrinology/oncology liaison meetings held at the UKCCSG offices in Leicester. The craniopharyngioma consensus was also additionally considered at 4 specifically dedicated workshops.

The membership and working group consisted of specialists in paediatric endocrinology, paediatric oncology, adult endocrine surgery, paediatric surgery, steroid biochemistry, radiotherapy, cancer genetics and paediatric neurology. Where a necessary sub-speciality expertise was not represented on the group, papers were circulated to specific experts nominated in the field (e.g. neuro-surgery, pituitary surgery, neuro-radiology, neuro-oncology, ophthalmology, neuro-endocrinology, molecular endocrinology) and to the specific speciality divisions of the UKCCSG, namely the CNS Tumour, Radiology and Radiotherapy Divisions.

At the 6 core workshops there was a brief (10 minute) introduction to each background paper, followed by rigorous debate (90 minutes per tumour section) and the agreed registering of the consensus view on the management of each specific tumour subtype. If more than one acceptable approach to management existed, these were incorporated as options of acceptable standards, thus resolving any disagreements. The configuration of service provision for this patient group was also considered and acceptable flow through schemes agreed. After the workshop the contributors of the background papers together with a nominated lead author, amended these on the basis of the discussions and circulated changes, through the chair, to all members of the wider group. Each tumour working group abbreviated the points to produce a concise consensus statement of the key issues and key recommendations for good practice. These were discussed at a further 5 meetings of the workshop members and circulated to all BSPED and UKCCSG members of the wider collaboration inviting comments and approval, and further to expert specialists in each field.

After agreement and completion by the Working Group, the guidelines were posted for a 5-week consultation period on both the BSPED and UKCCSG websites, with appropriate links and alerts to the whole membership, during which comments were invited and received. In addition, just prior to publication, the consensus statements were subjected to external review by five leading, international medical and surgical experts in the field (3 physicians, 1 surgeon, 1 geneticist), and also to the members of the Clinical Committee of the Society for Endocrinology. Each were asked for their agreement to the recommendations and any comments. The final version was agreed after 4 iterations. The craniopharyngioma section was additionally ratified by the members of the British Paediatric Neurosurgical Group (BPNG) and the CNS Tumour and Radiotherapy Divisions of the UKCCSG, whilst the whole document was endorsed by the Clinical Committee of the Society for Endocrinology (SfE). It was also sent for conconsideration to the guideline committee of the Royal College of Paediatricians and Child Health (RCPCH), whose approval is pending.

Types of Evidence for Consensus Recommendations

Due to the rarity of these tumours, it is recognised that level 1 or grade A or B evidence to support these recommendations is lacking; at best reports of best practice (level 2B/C) from well conducted clinical studies provide the evidence base. The recommendations are wherever possible, based on sound evidence of effectiveness from peer reviewed literature in academic journals and other related adult consensus guidelines where they exist. The latter include:

1. 'Pituitary Tumours; Recommendations for Service Provision and Guidelines for Management of Patients'; Royal College of Physicians (RCP), November 1997: ISBN: 1 86016 072 7
2. Guidelines for the Management of Thyroid Cancer in Adults, British Thyroid Association, Royal College of Physicians (RCP), March 2002: ISBN: 1 86016 157X
3. 'Guidelines for the Surgical Management of Endocrine Disease and Training Requirements for Endocrine Surgery', November 2000; from the British Association of Endocrine Surgeons (BAES)

Availability of Consensus Recommendations and Mechanisms for Updating

These guidelines were completed in October 2005 and are expected to be piloted over the next three years after which they will be re-evaluated for accuracy and content and modified if necessary.

They may be obtained in hard copy from the BSPED or UKCCSG or downloaded from the professional members' section of both the BSPED and UKCCSG websites accessed via the following links:

BSPED **http://www.bsped.org.uk**
UKCCSG **http://www.ukccsg.org**

Declarations of Interest - None declared

Introduction Summary for Consensus Recommendations

This consensus represents targets for clinical excellence. It is expected to evolve and be subjected to regular revision and audit and should be interpreted in the context of an individual patient's specific circumstances. Future revisions are expected to include ethically approved collection of minimum datasets for clinical and functional outcome, surgical and pathology reports and patient demographics. They will also encompass detailed patient information. These rare and complex tumours should only be treated effectively by multi-disciplinary teams in units familiar with their management.

Once the diagnosis of an endocrine tumour is suspected, patients should be referred to a specialist centre for further assessment and treatment. It is the view of the authors that all cases should be managed by a designated multidisciplinary team in a tertiary paediatric endocrine and collaborative UKKCSG centre, with access to appropriate specialist pathology, steroid endocrinology, genetic analysis and counselling, clinical oncology and relevant paediatric, neurosurgical or specific (eg endocrine) surgical expertise. These tumours though rare, are more common in adults. Paediatric specialists are encouraged to collaborate with their adult specialty colleagues managing the child in a paediatric or adolescent environment, under the care of qualified children's nurses, in accordance with the Children's National Standards Framework. Any peri-operative care should always involve paediatric endocrinologists, in collaboration with paediatric surgeons, paediatric oncologists and adult specialists as appropriate.

One paediatric speciality (usually endocrinology or oncology) should assume responsibility for the co-ordination of investigations, treatment, decision making, follow up and outcome assessment and oversee the registration to cancer and genetic registries and consent to tumour "banking". To this end there is a need for data on long term outcomes, tumour behaviour at the cellular level, mortality and morbidity of treatment, so that future treatment plans can be modified appropriately. Registers and accurate documentation held at national level are considered central to this objective, and have been agreed through the national childhood cancer registry of the UKCCSG. Patients up until the age of 21yrs with both benign and malignant endocrine tumours will be registered in this way and links to familial genetic cancer registries will be highlighted and established where appropriate.

Details for Patient Registration

All patients up to the age of 21 years, (and their families if relevant) should be notified to the Childhood Cancer Registry, UKCCSG, University of Leicester, 3rd Floor Hearts of Oak House, 9 Princess Road West , Leicester, LE1 6TH, using the attached form. *(Pages 12/13)*

Notification to other genetic registries should be undertaken by the regional genetics centre to which patients and their families may have been referred.

Details for Patient Registration

Please return to: Registry, UKCCSG, University of Leicester, 3rd Floor Hearts of Oak House, 9 Princess Road West, Leicester, LE1 6TH UK	**Childhood Cancer Registration**	Registry Number (please leave blank)

Surname / family name	Diagnosis
Forenames	Primary site Side : bilateral / right / left / midline / not applicable
Address Post code	Date of diagnosis age at diagnosis
Country of residence at diagnosis	Basis for diagnosis 1 histology / bone marrow 6 clinical 2 haematology 7 other 3 biochemistry 9 unknown 5 radiology
Place of birth	
Sex : male / female Date of birth	
Twin : 1 yes same sex / different sex 2 no	
Ethnic group 1 white 4 other / mixed (specify) 2 asian 5 oriental 3 black 6 middle eastern	Histology Cell markers : Fab classification : Philadelphia :
Registering hospital Treating hospital(s) Hospital number Consultant	*Please attach a copy of pathology report*
Referring hospital and consultant was patient treated at referring hospital? yes / no / not known Reason for referral to registering hospital 1 Referred at time of diagnosis / initial treatment mainly at registering hospital 2 Referred at relapse / recurrence / other illness 3 main treatment at referring hospital / registering hospital responsible only for follow up 4 Other (specify)	Pathologist and hospital Pathology lab number Stage – please specify staging system Highest pre-treatment leucocyte count at diagnosis x 10^9 / L Is this a second cancer? yes / no
Is patient in a clinical trial? yes / no Please specify which clinical trial If not in a trial, please specify reason why not *see list overleaf*	Congenital abnormality, genetic disorders & chronic diseases in patient

FATHER (biological)	MOTHER (biological)
Surname	Maiden name
Forenames	Forenames
Date of birth	Date of birth
Place of birth	Place of birth
Occupation at diagnosis	Occupation at diagnosis

COMMENTS

Please complete the table overleaf for family medical information
version 06/2001/2H

Please provide information about the diseases and disorders of the patient's family members in the appropriate boxes complete where you have the relevant information, otherwise mark the box 'not available'.

FAMILY DISEASES & DISORDERS	FATHER of patient	MOTHER of patient	BIOLOGICAL SIBLINGS Specify whether full or half-siblings Exclude adopted siblings
Congenital abnormalities Diseases Malignancies Other conditions			

	GRANDPARENTS of patient (Fathers parents)	GRANDPARENTS of patient (Mothers parents)
Congenital abnormalities Diseases Malignancies Other conditions		

	AUNTS, UNCLES, of patient (Fathers brothers & sisters)	AUNTS, UNCLES, of patient (Mothers brothers & sisters)
Congenital abnormalities Diseases Malignancies Other conditions		

	COUSINS of patient (Children of Father's brothers & sisters)	COUSINS of patient (Children of Mothers brothers & sisters)
Congenital abnormalities Diseases Malignancies Other conditions		

	OTHER RELATIVES of patient *please specify relationship to patient* (Fathers side of family)	OTHER RELATIVES of patient *please specify relationship to patient* (Mothers side of family)
Congenital abnormalities Diseases Malignancies Other conditions		

NOTE
RE: CLINICAL TRIALS (overleaf)
Please give one of the following reasons why the patient is NOT in a clinical trial:

a) No applicable trial
b) Not eligible
c) Clinical reasons
d) Does not wish to participate in trial
e) No specified reason
f) Patient deceased

Abbreviations

A_4	Androstenedione
ACT	Adrenocortical Tumours
ACTH	Adrenocorticotropin Hormone
ADH	Anti Diuretic Hormone
AFP	Alpha Foeto- Protein
ANP	Atrial or Brain Natriuretic Peptide
HCG	Human Chorionic Gonadotropin (beta subunit)
CAH	Congenital Adrenal Hyperplasia
CEA	Carcino Embryonic Antigen
CSW	Cerebral Salt Wasting
CT	Computerised Assisted Technology Scan
3D	Three-dimensional
DHEAS	Dehydroepiandrosterone sulphate
DDAVP	Desmopressin
DI	Diabetes Insipidus
DMSA	Dimethyl Succinic Acid
DTC	Differentiated Thyroid Cancer
ECG	Electrocardiogram
ENT	Ear, Nose and Throat
FAP	Familial Adenomatous Polyposis
FDG	^{18}Fluoro-deoxy-glucose
FSH	Follicle Stimulating Hormone
FHH	Familial Hypercalcaemic Hypocalciuria
FNA	Fine Needle Aspirate
FT_3	Triiodothyronine
FT_4	Thyroxine, Levothyroxine
GBq	Giga Becquerels
GnRH	Gonadotropin Releasing Hormone
Gsα	Stimulatory α subunit of the G-protein
IGF-1	Insulin-like Growth Factor-1
IGF-BP3	Insulin-like Growth Factor-Binding Protein-3
IM	Intramuscular
IV	Intravenous
Kg	Kilogram

LH	Luteinising Hormone
MDT	Multidisciplinary Team
MEN	Multiple Endocrine Neoplasia
MIBG	Meta-iodo-benzyl-guanidine
µg	Micrograms
mg	Milligrams
m^2	Square Metre of Body Surface Area
mmol/l	Millimoles per Litre
mU/l	Milliunits per Litre
MTC	Medullary Thyroid Carcinoma
MRI	Magnetic Resonance Imaging
NaCl	Sodium Chloride
NF-1	Neurofibromatosis Type 1
NICE	National Institute of Clinical Excellence
PPNAD	Pigmented Multinodular Adrenocortical Disease
PET	Positron Emission Tomography
PTH	Parathyroid Hormone
pTNM	Staged according to Tumour size, Node Metastases and distant Metastases
r-hGH	Recombinant Human Growth Hormone
r-hTSH	Recombinant Human Thyrotropin
SA	Surface Area
SCRT	Stereotactically Guided Conformal Radiotherapy (ie multiple fractions)
SDH	Succinate Dehydrogenase
17OHP	Seventeen Hydroxy Progesterone
SG	Specific Gravity
SHBG	Sex Hormone Binding Globulin
SIADH	Syndrome of Inappropriate ADH
SRS	Stereotactic Radiosurgery (ie single fraction)
Tg	Thyroglobulin
TSH	Thyroid Stimulating Hormone
UFC	Urinary Free Cortisol
VHL	Von-Hippel Lindau
XR	X-ray

CHAPTER ONE

Chapter One - Craniopharyngioma

1.1 Executive Summary of Proposed Management Pathway

Main Issues

Without class 1 evidence, management of craniopharyngiomas is complex and controversial. National registration and management by specialised multidisciplinary teams (MDTs), according to a preferred guideline will probably enhance survival, quality of care and inform future therapies.

The perception that it is a benign disease cured by aggressive surgical resection alone is not borne out by its often difficult and incomplete excision (90%), propensity to recur (25-75%) and - in older series employing repeated radical surgical approaches - its high late mortality (25-50%) and hypothalamo-pituitary, visual and cognitive morbidity (75%) when treated in this fashion.

Hypothalamic dysfunction causing morbid obesity and diabetes insipidus in conjunction with either adipsia or hypopituitarism is a profound cause of morbidity and mortality. It is thus an unacceptable post-operative result in a patient with previously intact hypothalamic function.

Adjuvant radiotherapy - even if used as salvage therapy - is highly effective at achieving long term tumour control. Its potential neurotoxicity, which may well be reduced by the use of recent focussed and stereotactic techniques, thus needs to be weighed against the significantly high morbidity and mortality of progressive or recurrent tumour and repeated radical neurosurgery.

Literature reviews suggest there are potentially two groups at risk extremes:

- good risk group (older children with small tumours (<2-4cm) and no hypothalamic syndrome or hydrocephalus),
- poor risk group (younger children with larger tumours (>2-4cm) and hypothalamic syndrome or hydrocephalus).

Complete tumour resection should only be considered in the good risk group, with adjuvant or salvage radiotherapy being used to treat residual or recurrent tumour and achieve long term tumour control according to the presented rationale and pathway.

Limited surgery is recommended for the high risk group with immediate (for older children) or delayed (for younger children) adjuvant post-operative radiotherapy, judged according to each individual's risk-benefit ratio.

CHAPTER ONE

Main Recommendations

The aims of treatment are to:
relieve raised intracranial pressure, optic and neurological compression,
preserve existing hypothalamic function and optic apparatus as a priority, even if this necessitates limited surgery and leaving residual tumour,
provide long-term tumour control even if a primary combined surgical and radiotherapeutic approach is required,
avoid second - look surgery and its unacceptably high morbidity and mortality,
minimise neurotoxicity including that caused by aggressive or repeated neurosurgical approaches, recurrent or progressive disease, as well as radiation,
effectively manage acute post-operative and long term salt and water balance, hypoadrenalism and the evolving, life-threatening pituitary deficits.

The aims of surveillance are to:
detect early recurrence,
facilitate age-appropriate growth and puberty, and optimise hormone substitution,
support neuro-rehabilitation and enhance long term independence and quality of life.

The aims of registration are to :
enhance treatment co-ordination, observational outcomes and future therapeutic trials.

Recommended Care Pathway; Child with Suspected Pituitary Tumour

Primary Care (GP/A&E)

↓

Secondary Care:
Paediatrician or one of several specialist services
Endocrinology, ophthalmology, neurology, neurosurgery, neuro-oncology

↓

MRI - Diagnosis of Pituitary Tumour Confirmed

↓

Paediatric Neuro-Oncology Centre
UKCCSG-affiliated neurosurgery with pituitary surgery and (neuro)endocrine expertise

Tertiary Multidisciplinary Team
Neurosurgeon,paediatric (neuro)endocrinologist, neuro-radiologist, radiotherapist, paediatric neuro-oncologist, (neuro)psychologist, ophthalmologist, neurologist, neuro-pathologist, (neuro)endocrine nurse specialist

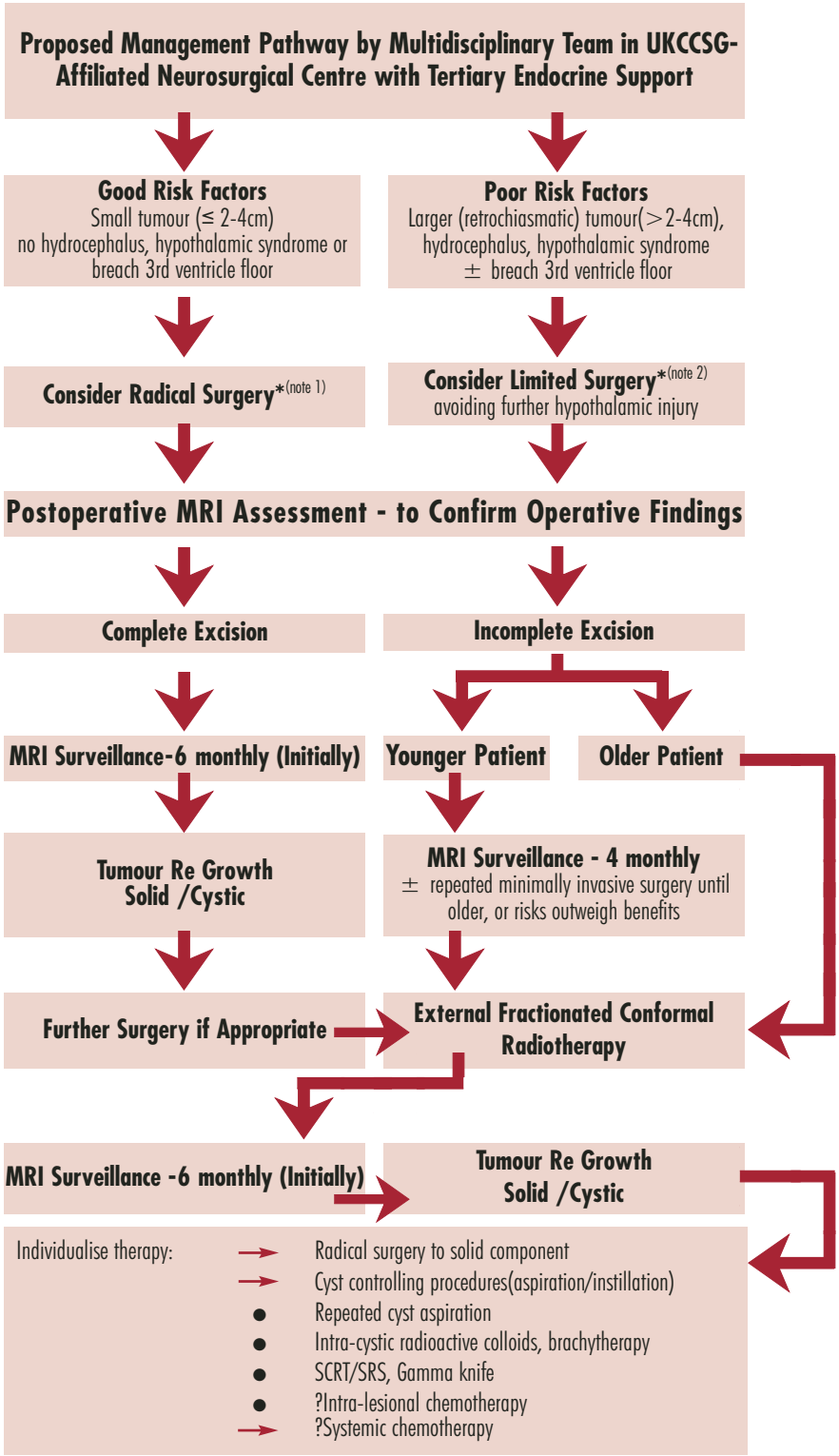
↓

Craniopharyngioma Confirmed

↓

Needs-Led, Lifelong Surveillance and MDT Support
according to patient age, tumour size, symptoms and recurrence history

Recommended Management Pathway: Child with Craniopharyngioma



Definitions and Surgical Notes for the Purpose of the Text on the Proposed Craniopharyngioma Management Pathway

Limited/Conservative surgery

This is the least invasive approach that minimises mortality and morbidity and relieves, but does not further compromise, visual and hypothalamic function. It includes endoscopic or stereotactic cyst aspiration, shunt procedures, transphenoidal approaches and open craniotomy to debulk those solid components **not** adherent to adjacent structures (hypothalamus, carotid artery, optic nerves) and work within the capsule. Since the aim is to minimise the trauma to these areas and/or reduce the required post-operative radiation field, accepting that complete removal is not possible without significant, largely hypothalamic, morbidity and mortality, **no** attempts to detach adherent capsule or finger-like projections from the hypothalamus should be made as previously advocated.
i.e. Limited resection = cyst drainage ± craniotomy for subtotal tumour resection, adequate to control symptoms without further compromise of visual pathways or hypothalamic structures

Complete Resection

In some cases it is accepted that the complete resectability of the tumour cannot be assessed pre-operatively, whatever the size, and this will require intra-operative assessment. The definition of a surgeon's perception of complete resection requires post-operative MRI confirmation of the absence of **all** capsular, cystic and solid portions of the tumour. Any remnants of these constitute a residuum.
i.e. Complete resection = radiologically confirmed on post-operative MRI scan

*surgical note 1

Consider transphenoidal resection in intrasellar tumours with patent air sinuses. Although complete resection is less likely, morbidity and mortality are lower with this technique.
Consider stereotactic aspiration of small cystic tumours to avoid craniotomy especially in the youngest children, until such time as definitive therapy is deemed necessary.

*surgical note 2

The surgical strategy may require a combination of strategies and/or staged procedures, including:
stereotactic or endoscopic aspiration of associated cysts,
relief of hydrocephalus with cyst aspiration or shunt procedures,
approach via open craniotomy depending on tumour position and surgeon's personal experience,
transphenoidal approach where a significant portion of the tumour is intrasellar or sub-diaphragmatic. This should be undertaken by a neurosurgeon with appropriate experience in this technique and a likely significant adult practice where this approach is more often indicated.

External Fractionated Conformal Radiotherapy

This is CT planned 3D conformal radiotherapy preferentially employing 3-6 non-coplanar beams.

Tumour Regrowth

This is defined by the primary treatment strategy:

After surgery alone - An increase in tumour (solid and/or cystic portion) on any post-operative MRI scans after baseline with or without deterioration in visual field perimetry.

After radiotherapy - An increase in solid and/or cystic component more than one year after radiotherapy, or a progressive increase on 2 consecutive MRI scans 4-6 months apart after post-radiotherapy baseline MRI with or without deterioration in visual field perimetry.

CHAPTER ONE

1.2 Introduction and UK Registry Data

Craniopharyngiomas:

These are slow-growing, congenital, mid-line, epithelial tumours arising embryologically from mal-development in the pituitary stalk or tuber cinereum (floor 3rd ventricle), which need differentiating from Rathke's pouch cysts.

Although rare (1-2 per million annually), they are the commonest mass lesion of the pituitary area in childhood[1,2,] constituting 6-13% of all childhood brain tumours and peaking at 5-10 years of age *(Table 1).*

Their benign histology belies their "malignant" tendency to local recurrence and invasion - with resulting pituitary, visual and hypothalamic morbidity[3,4,5,6,7,8] - requirement for oncological therapies and significant operative and late mortality (2%-38%) [6,9,10,11] *(Table 2).*

Their severity and rarity (15 new cases annually in children under 15years in UK) mandates central registration and prospective study of defined short and long-term outcomes after an agreed management plan, in a few highly specialised centres with the necessary multidisciplinary expertise.

Poor prognostic features are young age, hydrocephalus at presentation, hypothalamic involvement[3,12], a tumour height more than 4 cm in the mid-line[13,14] and a retro - chiasmatic tumour position[15].

Craniopharyngioma in National Registry of Childhood Tumours 1971-2002.

Table 1: Number of Registrations by Age and Sex.

	0-4years	5-9years	10-14years	Total
Male	55	115	109	279
Female	46	105	88	239
Total	101	220	197	518

Incidence rates were 0.9 per million at age 0-4 years, 1.8 at age 5-9 years, 1.6 at age 10-14 years and 1.4 years overall (age standardised). There was a small male excess at all ages.

Table 2: Actuarial Survival Rates (%) by Period of Diagnosis.

Time since diagnosis (years)	Period		
	1971-80	1981-90	1991-2002
1	82	96	98
2	78	94	95
3	75	94	95
5	69	91	93
10	61	84	89
15	55	78	
20	53	71	
25	52		
30	47		

1.3 Presentation

These patients present with acute, or more insidious, compression symptoms of adjacent neural structures, including:

- raised intracranial pressure with hydrocephalus (> 50% patients)
- visual impairment and field defects (scotomas and peripheral) paretic and non-paretic squints (30-60%)
- endocrinopathy, e.g. hypopituitarism (20-30%), growth and developmental failure (45-70%) [7,16,17] and diabetes insipidus (9-17%)
- hypothalamic dysfunction e.g. obesity or diencephalic syndrome (up to 30%) [7,16,17]
- incidental intra/suprasellar calcification on a skull X-Ray, with additional tumour evident on brain MRI or CT for unrelated purposes
- their differential diagnosis includes other sellar and suprasellar tumours (e.g. functioning and non-functioning pituitary adenomas, germinoma and non-germinomatous germ cell tumours), Rathke's pouch cysts and Langerhans Cell Histiocytosis and chiasmatic (low grade) gliomas.

1.4 Statement of Best Practice

For optimal outcomes, patients should be managed in a tertiary neuro-oncology and UKCCSG-affiliated specialist neurosurgical centre and discussed at a joint MDT meeting with the neuro-radiologist, paediatric endocrinologist, radiation oncologist, neuro-oncologist and, wherever possible, a neuro-psychologist.

The operation should be attempted only by experienced paediatric neurosurgeons nominated to undertake this procedure in each centre by the MDT. They should have ready access to pituitary microsurgery and/or transphenoidal expertise and an adult skull-based neurosurgical team, with readily available tertiary paediatric endocrine support from diagnosis.

1.5 Diagnosis and Emergency Stabilisation

Adequate imaging [18,19,20] is necessary to establish the likely diagnosis.

Children should be stabilised prior to transfer to a tertiary UKCCSG-affiliated neurosurgical centre with paediatric endocrine expertise.

Timed random and 08.00-09.00h serum cortisol measurements and paired early morning plasma and urine electrolytes, glucose and osmolalities should be performed prior to commencement of any dexamethasone therapy.

βHCG and AFP tumour markers should be considered, to exclude secreting germ cell tumours, with the result available **before** surgery.

Prolactin measurement is also required **pre-operatively** to exclude a prolactinoma.

1.6 Pre-Operative Management

i. Imaging:

In urgent cases or for patients in whom MRI is not feasible, a CT scan is acceptable, for the assessment of the emergency relief of raised intracranial pressure.

CT may show intra- and supra-sellar calcification, ballooning of the pituitary fossa, erosion of the sella turcica and features of raised intracranial pressure, and may occasionally be diagnostic.

MR scanning is preferable to CT as it provides better anatomical definition and is required prior to any necessary surgical intervention. It is more likely to distinguish craniopharyngioma from other causes of mass lesions of the pituitary region. This should be done in a centre with experience.

Imaging of the whole head is important for the evaluation of hydrocephalus and initial assessment. For small tumours (<2 cm), additional dedicated imaging of the pituitary region is helpful in providing greater anatomical detail.

ii. Pre-Operative Specialist Investigations

Since raised intracranial pressure is frequent and may require urgent intervention, there may be little opportunity for specialist investigations.

Where possible, specialty referrals and baseline assessments of the child's ophthalmology (visual acuity and fields ± colour vision), basal endocrinology, psychology and neurology should be performed.

Pre-operative auxology and endocrine biochemistry should include where possible, the measurement of:

- height, weight, surface area, pubertal ratings and bone age,
- serum thyroid hormones, (FT_4 ± FT_3 and TSH) to assess possibility of secondary hypothyroidism,
- plasma 07.00h, 08.00h, and/or 09.00h cortisol (if not on dexamethasone) as a guide to pre-operative adrenal reserve,
- paired early morning urine and plasma osmolalities, electrolytes and glucose to assess likelihood of diabetes insipidus and potential for hypo- or hyper-glycaemia,
- insulin-like growth factor-1 (IGF-1) ± its binding protein ($IGF\text{-}BP_3$) as a measure of pre-operative growth hormone status,
- serum gonadotrophins (LH and FSH) in infants (<2yrs) or peri-pubertal children (>8yrs) as a measure of pre-operative hypothalamic GnRH activity,
- **if the patient is on growth hormone this should be stopped prior to surgery.**

iii. Objectives of Treatment

These include:

- relief of raised intracranial pressure,
- reversal of visual and neurological compression symptoms,
- restoration of, or substitution for, specific hormone / system deficits,
- preservation of existing hypothalamic function,
- prevention of tumour re-growth / progression,
- reduction of long term morbidity and mortality.

iv.

Therapeutic options and their likely outcomes

In the absence of consistent registration or prospective multi-centre trials, the best definitive individual management approach is unclear.

There are two major treatment approaches, which require consideration by the MDT. These are

- radical resection to effect a surgical cure, with or without adjuvant radiotherapy to reduce recurrence

or

- subtotal resection with early or later (at re-growth) adjuvant radiotherapy.

a.

Complete Radical Resection with or without Adjuvant Radiotherapy

Given that the tumour is histologically benign, complete radical resection offers the best chance of cure, recurrence after a radiologically confirmed complete resection being 5% at 0.5-5years[13] but 20-25% with longer follow-up [15,21].

This strategy additionally avoids potentially neurotoxic cranial irradiation which aggravates any pre-existing endocrinopathies, may predispose to second malignancies and results in an age- and dose-dependent cognitive impairment.

However, despite radical surgical intent, few tumours are radiologically completely excised, this likelihood decreasing with increasing tumour height in the mid-line *(Table 3)*

Table 3: Likelihood of Achieving Radiological Complete Resection after Radical Intent [13,21]

Tumour height in mid-line	< 2cm	<4cm	>4cm
Percent completely resected	90%	60-90%	0%
Recurrence rate (0.5-5yr)	5-25%		75-80%

Those tumours more then 4cm in mid-line[13] particularly if retro-chiasmatic[15], or supra-diaphragmatic breaching the floor of 3rd ventricle, are unlikely ever to be completely excised, and carry a greater recurrence (75-80%) risk [14,15].

40-50% of craniopharyngiomas are larger than 3 cms in the mid-line[3,13] encroaching on the hypothalamic area and attempting surgical cure carries unacceptably high rates of (>50%) post-operative hypothalamic morbidity[7,15,16,21], operative (2.5%-10%) [6,15] and late (11-28%) mortality[6,13,15,18] which both correlate with the number of surgical interventions, (young) age, the degree of hydrocephalus, hypothalamic involvement, tumour height (>3.5cm) in the mid-line, tumour location and brain invasion, and hence attempts to detach tumour from the hypothalamic area.[3,5,6,8,13] In such 'poor risk' cases a more conservative surgical approach is recommended.

Hypothalamic morbidity results in hyperphagia, uncontrollable obesity, adipsia, behavioural and cognitive deficits, loss of temperature control, somnolence and early death (11% late surgical mortality). These sequelae are unacceptable in patients with intact hypothalamic function preoperatively and account for some of the late mortality seen in 10- and 20-year survival figures.

By contrast, tumours smaller than 2cm in the mid-line, are likely to be successfully (90%) resected[13] (or marsupialised), but still carry a 5-25% recurrence risk in 0.5 - 5 years[13,21]. Early adjuvant radiotherapy reduces the recurrence risk further (to 2-10%) *(table 4)*, but this has to be weighed up against the "unnecessary" exposure of the majority (75%), to a potentially neurotoxic radiation modality.

b.

Combined Modality Treatment; Limited Surgery and Immediate or Delayed (in the case of younger children), Adjuvant Radiotherapy

Given the difficulties in achieving surgical cure in 'poor risk' cases and the tumour's high propensity (50% -100%) [10,13,21,22] to quickly recur after incomplete surgical excision - 100% within 9 months in one series[22] and depending on the extent of resection[13] and length of follow-up [21] - early adjuvant focussed conformal radiotherapy is recommended for residual disease. This approach not only achieves long term control in the majority (70-80%), reducing recurrence rates from 75%-100% to 16-25% with no greater detriments in long term morbidity and mortality[3,10,19,21,22], but also potentially avoids second attempts at curative surgery which carries significantly greater morbidity and mortality from adipsia or hypothalamic hypopituitarism than primary surgery (10-50% [12,13,18,21] vs 1.1-2.5% [13,25]).

After gross total resection, there remains a significant long term risk of tumour re-growth. This varies between 5-25%[2,4] when complete resection has been radiologically confirmed and up to 41% and 53% at 5 and 10 years respectively[22] in series where extent of resection was assessed at operation alone. Practice varies from routine post-operative radiotherapy to reduce this risk[10,24,26] to withholding external irradiation until recurrence is apparent[6,15,21,23]. The lack of demonstrable difference in progression-free survival after radiotherapy for both incompletely and completely excised tumours, suggests that radiotherapy is effective in controlling the progression of microscopic as well as macroscopic residual disease.[24] Salvage radiotherapy is effective, with 10 year survival rates (77-85%) being similar whether radiotherapy is applied early post-operatively or delayed for disease recurrence[9,11,22]. However this may be at the expense of functional outcome and long term degradation in 20 year survival *(Table 4)*.

Table 4. Recurrence Rates after Complete and Incomplete Resection ± Adjuvant Radiotherapy

5 year recurrence	Complete resection	Incomplete resection (Subtotal/Partial)
Surgery alone	15.6% [13] 5 -25% [21] 58% [22]	75% [13] (49% - 87%) [22]
Surgery and adjuvant radiotherapy	2 -10% [24]	25% [24] 16% [22]

Thus a balance must be made between the hypothalamic morbidity and mortality of repeated surgical interventions, and the potential neurotoxicity of adjuvant cranial radiotherapy for residual or relapsed disease. This includes optic neuropathy, hypothalamo-pituitary failure and neurological and cognitive impairment. However, hypothalamic damage, which can result in premature death from morbid obesity, adipsic diabetes insipidus and/or pituitary failure[7], correlates with age, presenting symptoms, extent of surgery, and hypothalamic invasion[3,4,12,22] but not irradiation. In addition, the few available studies suggest neuropsychological deficits occur even in the absence of cranial irradiation[19,27] and it remains possible that delaying radiation in the youngest children on the unproven assumption that recurrent disease and the surgery required is **less** neurotoxic than new focussed irradiation techniques to prevent relapse, may deprive these children of an early cure and quicker neuropsychological rehabilitation. This hypothesis requires testing.

There is virtually no evidence base to support the role of systemic chemotherapy[28] or cystic sclerotherapy as first line therapy, in lieu of focussed radiotherapy, or suggest their neurotoxicity in the very young is substantially less. Intra-cavity injection of radio-labelled beta emitters (^{90}Y, ^{32}P) [29,30,31] or bleomycin for predominantly cystic lesions [30,32,33,34] using stereotactic techniques has some limited application to reduce tumour size, (50% reduction in 50% cases when used with repeated cyst aspirations), but at the expense of local and/or systemic toxicity in 10-40% which is potentially severe in 20%. The latter appears dose-dependent and includes infarct/haemorrhage (10%), somnolence (15%) and even death (0-3%) after bleomycin. There is little dose consensus.

The place of stereotactic radiosurgery [29,35,36] for solid tumours smaller than 20 mm, where critical structures are 5 mm from high dose region[37], requires further study but may have less success in children due to their different histology[29].

1.7 Operative Management *(see earlier proposed management pathway)*

Preserving hypothalamic function and thus reducing late morbidity and mortality is one of the most important aims of treatment.

Unless pre-operative assessment suggests a tumour amenable to total resection **without** additional hypothalamic compromise (e.g. less than 2cm in mid-line), a policy of limited surgical resection is recommended even if this leaves residual tumour.

In young children, minimally invasive conservative surgery and close observation where possible are advised. A'cut-off' age is not specified. Although 5 years has been suggested it is not appropriate to make a general recommendation. This needs careful consideration with the family and the MDT according to the characteristic risk-benefit profile of each individual case.

Acutely raised intracranial pressure or pending visual failure will require early surgical decompression. A 2-stage procedure may be beneficial[8,13].

Transphenoidal surgery should always be considered where possible, e.g. in sub-diaphragmatic tumours with fully aerated sinuses[13,16] but open craniotomy may well be necessary in cases where macroscopic complete excision is the treatment of choice.

1.8 Peri-Operative Medical Management *(see appendix 1)*

Prior knowledge of paired early morning urine and plasma electrolytes (osmolalities and glucose) and liaison with the anaesthetist and endocrinologist are essential.

High dose dexamethasone therapy is frequently used for cerebral oedema, in which case no further operative steroid cover is required. Otherwise, until/unless adrenal competence is established, hydrocortisone in stress doses (2 mg/kg of body weight, IM / IV), should be administered with induction. For operations exceeding 4 hours a further bolus of hydrocortisone will be required during the procedure.

It should be noted that ACTH deficiency may conceal diabetes insipidus (DI) and cortisol replacement unmask it. If the patient has DI at presentation, desmopressin should be administered prior to surgery. In the intra-operative period, fluid intake should be carefully monitored and adjusted so that fluid balance is maintained (with an allowance of 300ml/m^2/day for insensible loss) and excess fluid losses are replaced volume for volume.

Peri-operative hormonal treatment should be undertaken in consultation with a paediatric endocrinologist.

Peri-operative fluid balance, and the need for desmopressin, should be undertaken in consultation with a paediatric endocrinologist according to agreed guidelines *(appendix 1)*. A proportion of patients (9-17%) will have pre-operative diabetes insipidus[7,17] and more will have evidence of this post-operatively[16].

If seizures are biochemically induced, correction of this biochemical abnormality may obviate the need for anticonvulsant medication.

If anti-convulsants are used, awareness of their impact on fluid balance, potentiating the effect of desmopressin, (e.g. carbamazepine[38] and lamotrigine[39]) is important.

Precautions in monitoring fluid balance, associated diabetes insipidus, cerebral salt wasting and thirst disorders must be taken *(see appendix 1)*.

1.9 Histopathology

Neuro-histopathology should confirm the diagnosis and, in particular, exclude a low grade glioma, Rathke's pouch cyst, Langerhans Cell Histiocytosis or germinoma. Rathke's pouch cysts require drainage and marsupialisation only and are less likely to recur, so that an observation policy can be recommended.

1.10 Post-Operative Management

i. External Irradiation

Based on a national consensus and given that salvage radiotherapy achieves similar local control rates as ''upfront'' irradiation, adjuvant radiotherapy in radiologically confirmed completely excised craniopharyngiomas is not advocated unless cystic/solid tumour regrowth occurs during follow-up.

By contrast, immediate postoperative conformal fractionated radiotherapy should be considered for incompletely excised disease in older patients[3,13], after which recurrence rates are low [3,8,13,22,24,25,26].

Adjuvant radiotherapy to subtotally resected tumours may be delayed in very young children if the balance of harm from adjuvant radiation is deemed greater by the MDT than that from tumour re-growth and/or second surgery. A holding strategy - in which cyst control is achieved with minimally invasive surgical procedures/aspirations and monitored with 4-monthly ophthalmic and MRI surveillance - may suffice until the child is either deemed old enough for radiotherapy, or the risks of its omission outweighs the benefits.

Tumour doses in the range of 50 to 54 Gy in 30 to 33 fractions (≤ 1.8 Gy per fraction) have been recommended [9,11,40] in all children regardless of their age. There is no consensus on the target volume requiring treatment or its margin[40], and whether this should be the residual solid/cystic disease or the whole postoperative tumour bed. Single fraction radiosurgery offers no advantage over conventional external beam fractionated irradiation and can only be considered for a few, very selected patients with small spheroid tumours (≤3.5 cm and more than 3-5 mm away from the optic apparatus and brainstem)[41,42,43,44]. Radiosurgery for larger craniopharyngiomas using multiple isocentres in conjunction with intracystic radioisotopes or bleomycin instillations cannot be recommended because of the very high recurrence rates (up to 82%) [43].

It is recommended that CT planning using 3D conformal techniques are used. Where available, CT/MRI fusion should be performed to improve target volume definition. Children should be treated supine, with a linear accelerator, in a custom-made, purpose-built immobilisation device. The gross tumour volume definition (GTV) should be based on information derived from pre- and post-operative CT and MRI scans and should encompass the entire tumour bed as well as the residual tumour (solid and cystic) with an additional margin defined according to departmental policies[25,40]. If available, fractionated stereotactic conformal radiotherapy should be employed as it further reduces the amount of normal brain encompassed in the high dose irradiation volume.

ii.

a.

Surveillance

Short term - 2 post-operative weeks

Diabetes insipidus occurs in over 90% patients immediately post-operatively and is permanent in 60%-80%[3,16]. Its association with hypodipsia and hypoadrenalism is particularly dangerous and a significant cause of late mortality[3,12,15,21]. Its potentially complex management should be undertaken in conjunction with a paediatric endocrinologist according to the suggested guideline *(appendix 1)*. Persistence beyond 7 post-operative days suggests permanent diabetes insipidus.

Early assessment of cortisol requirement is difficult to perform before discharge from the neurosurgical ward if the patient has been receiving peri-operative dexamethasone. It is usual for most patients to receive glucocorticoid replacement therapy until the first post-operative provocation test of glucocorticoid reserve, some 6-12 weeks after surgery.

Post-operative complications other than diabetes insipidus occur in 10% - 25% patients; recurrent surgery increases this risk. They include cerebro-spinal leaks, meningitis, sinusitis and seizures[13,16,18] which require management according to local practice/guidelines.

An immediate post-operative (24-72h) MRI scan to determine the presence of residual tumour, hydrocephalus or treatment related complications is considered best practice *(table 5)*.

Table 5 Suggested Radiological Surveillance Strategy
In the absence of clinical symptoms, post-operative MRI surveillance scan recommendations are dependent on the primary treatment strategy:

Primary Treatment Strategy

	Complete Resection (confirmed)	Limited Surgery with Post-Operative Surveillance	Limited Surgery with Adjuvant Radiotherapy
Radiological Assessment	Frequency	Frequency	Frequency
First Post-Interventional Baseline MRI Scan	MRI at 24-72 h post-intervention ± CT to assess possibility of residual calcified capsular rim	MRI at 24-72 h post-intervention ± CT to assess possibility of residual calcified capsular rim	MRI at 24-72 h post-intervention ± CT to assess possibility of residual calcified capsular rim
3 month post-operative MRI scan	MRI at 3 months	MRI at 3 months	MRI at 3 months
Frequency in first 2 years	6-monthly MRI	4 monthly MRI	Annual MRI
Frequency in years 3-5	Annual MRI	6-monthly MRI	Annual MRI
Frequency after 5 years	MRI at clinician's discretion	Annual MRI	MRI at clinician's discretion

b.

Medium to Long Term - 4 Post-Operative Weeks to Lifelong *(table 5 and 6)*

Visual assessment: Early post-operative visual fields and acuity with or without contrast sensitivity in colour vision (whose sensitivity is under investigation) should be assessed[13,15] regularly every 2-3months for the first 2 years, 6-12 monthly for the next 3 years and 1-2 yearly thereafter until stable. Deterioration, particularly in acuity, requires exclusion of tumour regrowth or cystic degeneration[18].

Radiological: Whole head imaging at 3 post-operative months is helpful for comparative assessment with the immediate post-operative scan. Dedicated pituitary region studies are best to provide higher anatomical detail for small lesions. The necessity and frequency of later scans is uncertain, but both early and late (>5years) tumour regrowth is less common after radiotherapeutic than surgical cure[45]. Thereafter, excepting very young children in whom a delayed curative radiotherapeutic strategy needs monitoring by 4-monthly surveillance MRI for 2 years, 6-monthly for a further 3 years and annually thereafter, the suggested schedule depends on the primary treatment strategy and the absence of clinical symptoms. In those with an apparent surgical cure, scans are recommended 6-monthly for 2 years and then annually for at least a further 3 years, whilst those with a radiotherapeutic cure require less intensive monitoring annually for 2 years and 12-18monthly for at least a further 3 years depending on clinical circumstances[45] *(appendix 2)*.

Endocrinological: Most patients usually receive glucocorticoid cover until a provocation test of glucocorticoid (and growth hormone) reserve, is performed 6-12 weeks post-operatively. Improvement or normalisation of pre-operative pituitary hormone dysfunction may occur and requires assessment. A persisting deficiency at 12 weeks is likely to be permanent. In the **absence** of adjuvant radiotherapy, which itself induces an evolving pituitary endocrinopathy, new pituitary deficiencies suggest tumour regrowth.

The endocrinopathies incurred after pituitary surgery and external irradiation are common (70-100%) and most marked in the first 2 post-operative years, slowly progressing thereafter. These are unlikely to be solely irradiation-induced. In the absence of pituitary surgery for pituitary mass lesions, only 50% of irradiated childhood and adult patients have some degree of hypopituitarism 20 years later[10]. Lifelong hormonal follow-up is required; the optimal intervals are unknown but 6-monthly clinical assessments to adult height are required, with regular neuro-endocrine review in adulthood.

Table 6 Suggested Short and Long term Clinical Surveillance Strategy
Underlined text indicates suggested clinical lead physician(s) although it is recognised that many children treated in neuro-oncological centres will be seen in a MDT setting

Primary Treatment Strategy

	Complete Resection (confirmed)	Limited surgery with Post-Operative Surveillance	Limited Surgery with Adjuvant Radiotherapy
Clinical Assessments			
Post-operative	Endocrine Psychological	Endocrine Psychological	Endocrine Psychological
Frequency in first 2 years	Neurosurgical 3-monthly Endocrinological 3-6 monthly Ophthalmologic 3-6 monthly Psychological at 2 Years	Neurosurgical 2-monthly Endocrinological 3-6 monthly Ophthalmologic 3-4 monthly Psychological at 2 Years	Clinical Oncology 3-monthly Endocrinological 3-6 monthly Ophthalmologic 6-12 monthly Psychological at 2 Years
Frequency in years 3-5	Neurosurgical 6-12 monthly Endocrinological 6-monthly Ophthalmologic 6-12 monthly Psychological at Year 5	Neurosurgical 4-6 monthly Endocrinological 6-monthly Ophthalmologic 6 monthly Psychological at Year 5	Clinical Oncology 6-12 monthly Endocrinological 6-monthly Ophthalmologic 6-12 monthly Psychological at Year 5
Frequency after 5 years since last therapeutic intervention	Endocrinological 6-monthly till adult height annually till adult transfer 1-2 yearly subsequently Psychology at 18 Years for career guidance	Neurosurgical at clinician's discretion Endocrinological 6-monthly till adult height annually till adult transfer 1-2 yearly subsequently Psychology at 18 Years for career guidance	Clinical Oncology annually Endocrinological 6-monthly till adult height annually till adult transfer 1-2 yearly subsequently Ophthalmic 1-2 yearly Psychology at 18 Years for career guidance

1.11 Tumour Regrowth (cystic or solid)

The treatment of recurrent disease is likely to include radiotherapy if not previously used and should be used with caution in the youngest children after demonstrable tumour progression.

The treatment of cystic recurrences needs to be individualised and may entail repeated surgical drainage, intra-cavity installation of radioactive isotopes (^{90}Y ^{32}P ^{186}R)[29,31] or chemotherapy using bleomycin[33,34]. The latter two options may cause significant optic nerve and cerebrovascular toxicity and such service provision should be limited to selected centres. Systemic chemotherapy has also been anecdotally described but is currently perceived as experimental[47,48]. No optimal therapy for these situations has been defined so far.

1.12 Long Term Care and Surveillance

Follow-up is best co-ordinated by the MDT in a neuro-endocrine setting with input from specialists in neurosurgery, radiotherapy, ophthalmology, neuro-oncology, neurology and psychology *(table 6)*

2-3 months after the completion of definitive treatment (surgery with/without radiotherapy), a full assessment of the hypothalamo-pituitary-target gland axes should be undertaken with caution, off steroids, in a dedicated paediatric endocrine centre.

Adult endocrine transition and assessment will be required for essential life-long follow-up, preferably in an endocrine centre with similar associated pituitary neurosurgical, neuropsychological and neuro-oncological support. Reproductive or gynaecological/urological advice should be sought early. Patients should be seriously considered for continuing adult growth hormone *(r*-hGH*)* replacement therapy and registered as such with the relevant endocrine society according to NICE guidelines.

1.13 Management of Endocrine and Hypothalamic Morbidity

This includes the careful management of:

- hypothalamic disorders of thirst, appetite, temperature and sleep control, which can precipitate crises in fluid balance and premature death during intercurrent illness[3,7,21] *(appendix 1)* .
- hypo-adrenal crises in association with intercurrent illness; these are potential contributors to morbidity and mortality. The importance of repeated instruction to increase steroid replacement doses at times of illness, and warning adolescents about the potent hypoglycaemic effects of alcohol are emphasised[1].
- obesity, which may ultimately compromise cardiovascular and pancreatic function and reduces self-esteem[12].
- re-establishment of normal statural growth, with titration of *r*-hGH replacement therapy and pubertal induction.
- maintenance of sexual maturation with the initiation and gradual increase in sex steroid replacement.
- other major sequelae of neurological impairment, such as hemiplegia, combined with and aggravating obesity and immobility with resulting osteoporosis and fractures.
- blindness or partial sightedness, severe psycho-pathological and educational needs and career guidance[12,19,27].

1.14 Registration and Tumour Banking

Notification to the National Childhood Cancer Registry, UKCCSG by the neuro-oncologist is strongly recommended. Consent to tumour banking as per UKCCSG protocol is encouraged.

1.15 Information and Support for Patients and Carers

Patients may find the following web-sites and contact organisations useful:

- Child Growth Foundation
  2 Mayfield Avenue, Chiswick, London W4 1PW
  Telephone: +44 (0)20 8995 0257 Fax: +44 (0)20 8995 9075
  Email: cgflondon@aol.com; website; **http://www.childgrowthfoundation.org/**

- The Pituitary Foundation
  PO Box 1944, Bristol, BS99 2UB;
  Telephone/Fax: 0845 450 0375
  E-mail: helpline@pituitary.org.uk; website; **http://www.pituitary.org.uk/disorders/**

References

1 Sanford R A, Muhlbauer M S. Craniopharyngioma in children. Neurologic Clinics, 1991; 9: 453-65.

2 Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM. The descriptive epidemiology of craniopharyngioma . J Neurosurg 1996; 89: 547-51.

3 De Vile C, Grant DB, Kendall BE, Neville BGR, Stanhope R, Watkins KE, Hayward RD. Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? J Neurosurg 1996; 85: 73-81.

4 Poretti A, Grotzer MA, Ribi K, Schonle E, Boltshauser E. Outcome of craniopharyngioma in children: long term complications and quality of life. Developmental Medicine and Child Neurology 2004 : 46 : 220-9

5 Hoffman HJ, DeSilva M, Humphreys RP et al. Aggressive surgical management of craniopharyngiomas in children. J Neurosurg 1992; 76: 47-52.

6 Yasargil M G, Curcic M, Kis M, Siegenthaler G, Teddy P J, Roth P. Total removal of craniopharyngiomas: approaches and long-term results in 144 patients.J Neurosurg,1990; 73: 3-11

7 De Vile CJ, Grant DB, Hayward RD, Stanhope R. Growth and endocrine sequelae of craniopharyngioma. Arch Dis Child 1996; 75: 108-14.

8 Hayward RD, Devile C, Brada M. Craniopharyngioma In: 'Brain and Spinal Tumors of Childhood'. Walker DA, Perilongo G, Punt JAG & Taylor RE (eds); Arnold (pubs), 2004 pp 370-86

9 Schulz-Ertner D, Frank C, Herfarth KK, Rhein B, Wannenmacher M, Debus. Fractionated stereotactic radiotherapy for craniopharyngiomas. Int J Rad Oncol Biol Phys 2002; 4: 1114-1120

10 Brada M, Rajan B, Traish D, Ashley S et al. The long term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas . Clin Endocrinol 1993; 38: 571-8.

11 Habrand JL, Ganry O, Couanet D, Rouxel V, Levy-Piedbois C, Pierre-Kahn A, Kalifa C. The role of radiation therapy in the management of craniopharyngioma: a 25 year experience and review of the literature. Int J Rad Oncol Biol Phys 1999; 44: 255-63.

12 De Vile C J, Grant D B, Hayward R D, Kendall B E, Neville B G R, Stanhope R. Hyperphagia and obesity in childhood craniopharyngioma: relation to post-operative hypothalamic damage shown by magnetic resonance imaging. J Clin Endocrinol Metab 1996; 81: 2734-2737.

13 Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M. Surgical treatment of craniopharyngiomas: experience with 168 patients. J Neurosurg 1999; 90: 237-50.

14 Hetelikidis S, Barnes PD, Tao ML et al. Twenty year experience in childhood craniopharyngioma. Int J Rad Oncol Biol Phys 1993; 27: 189-95.

15 Van Effenterre V, Boch AL. Craniopharyngioma in adults and children: a study of 122 surgical cases. J Neurosurg 2002: 97: 3-11.

16 Honegger J, Buchfelder M, Fahlbusch R. Surgical treatment of craniopharyngiomas: endocrinological results. J Neurosurg 1999; 90: 251-7.

17 Sklar C A. Craniopharyngioma: endocrine abnormalities at presentation. Pediatric Neurosurgery, 1994; 21 (supplement 1): 18-20.

18 De Vile CJ. A follow-up study of the outcome of children post-craniopharyngioma surgery. MD Thesis University of London 1998.

19 Cavazzuti V, Fischer EG, Welch K, Belli JA, Winston KR. Neurological and psycho-pathological sequelae following different treatments of craniopharyngioma in children. J Neurosurg 1983; 59: 409-17.

20 Savoiardo M, Ciceri E. Neuroradiology of craniopharyngiomas. In: Broggi G, ed. Craniopharyngioma: Surgical Treatment. Milan: Springer-Verlag, 1995: 719.

21 Bin-Abbas B, Horia Mawlawi, H, Sakati N, Khajafa Y, Chadhary MA, Al-Ashwal A. Endocrine sequelae of childhood craniopharyngioma, J Pediatr Endocrinol Metab 2001; 14: 869-74.

22 Stripp DCH, Maity A, Janss AJ, Belasco JB, Tochner ZA, Goldwein JW, Moshang T, Rorke LB, Phillips PC, Sutton LN. Surgery with or without radiation therapy in children and young adults. Int J Rad Oncol Biol Phys 2004; 58: 714-7120.

23 Hoffman H J. Surgical management of craniopharyngioma. Pediatric Neurosurgery, 1994; 21 (supplement 1): 44-49.

24 Rajan B, Ashley S, Groman C, Jose CC, Horwich A, Bloom HJG, Marsh H, Brada M. Craniopharyngioma: long term results following limited surgery and radiotherapy. Radiotherapy and Oncology 1993; 26: 1-10.

25 Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, Lustig RH, Kun LE. Craniopharyngioma: the St Jude children's research hospital experience 1984-2001. Int J Rad Oncol Biol Phys 2002; 53: 533-542.

26 Brada M, Thomas D G T. Craniopharyngioma revisited. Int J Rad Oncol Biol Phys 1993; 27: 471-475.

27 Carpentieri SC, Waber DP, Scott M, Goumnerova LC, Kieran MW, Cohen LE, Kim F, Billett AL, Tarbell NJ, Pomeroy SL. Memory deficits among children with craniopharyngiomas. Neurosurgery 2001; 49: 1053-7.

28 Lippens RJJ Rotteveel JJ, Otten BJ, Merx H. Chemotherapy with adriamycin (doxorubicin) and CCNU (lomustine) in four children with recurrent craniopharyngioma. Eur J Pediatr Neurol 1998; 2: 263-8.

29 Lunsford L D, Pollock B E, Kondziolka D S, Levine G, Flickinger J C. Stereotactic options in the management of craniopharyngioma. Pediatric Neurosurgery 1994; 21 (supplement 1): 90-97.

30 Jiang R, Liu Z, Zhu C. Preliminary exploration of the clinical effect of bleomycin on craniopharyngiomas. Stereotact Funct Neurosurg 2002; 78: 84-94.

31 Voges J, Sturn V, Lehrke R, Treuer H, Gauss C, Berthold F. Cystic craniopharyngioma: long term results after intracavitary irradiation with stereotactically applied colloidal beta-emitting radioactive sources. Neurosurgery 1997; 40: 263-70.

32 Hader WJ, Steinbok P, Hukin J, Fryer C. Intratumoral therapy with bleomycin for cystic craniopharyngiomas in children. Pediatr Neurosurg 2000: 33: 211-8.

33 Mottolese C, Stan H, Hermier M, Berlier P, Convert J, Frappaz D, Lapras C. Intracystic chemotherapy with bleomycin in the treatment of craniopharyngiomas. Childs Nerv System 2001: 17; 724-30.

34 Park DH, Park JY, Chung YG, Lee HK, Lee KC, Suh JK. Outcome of postoperative intra tumoral Bleomycin injection in cystic craniopharyngioma. J Korean Med Sci 2002; 17: 254-9.

35 Kobayashi T, Tanaka T, Kida Y. Stereotactic gamma radiosurgery of craniopharyngiomas. Pediatr Neurosurg 1994; 21: 69-74.

36 Jackson IM, Noren G. Gamma knife radiotherapy for pituitary tumours. Baillieres Best Pract Res Clin Endocrinol Metab 1999 Oct ; 13

37 Reda WA, Hay AA, Ganz JC. A planned stereotactic approach for cystic intracranial tumours. Report of two cases. J Neurosurg 2002; 97 (5 Suppl): 610-2.

38 Van Amelsvoort T, Bakshi R, Devaux CB, Schwabe S. Hyponatraemia associated with carbamazepine and oxcarbazepine therapy; a review. Epilepsia 1994; 35: 181-8.

39 Mewasingh L, Aylett S, Kirkham F, Stanhope R. Hyponatraemia associated with lamotrigine in cranial diabetes insipidus. Lancet 2000: 356: 656 (case report).

40 Jephcott CR, Sugden EM, Foord T. Radiotherapy for craniopharyngioma in children : A national audit. clin oncol (R Coll Radiol) 2003 Feb ; 15 (1) : 10-3.

41 Mokry M .Craniopharyngiomas .A six year experience with Gama Knife radiosurgery. Stereotactic Funct Neurosurg 1999 ; 72 (Suppl 1) : 14-9.

42 Chung WY, Pan D H-C, Shiau C-Y, Guo W-Y, Wang L-W. Gamma knife radiosurgery for craniopharyngiomas. J Neurosurg 2000 ; 93 (Suppl 3) : 47-56.

43 Ulfarsson E, Lindquist C, Roberts M, Rahn T, Lindquist M, Thoren M, Lippitz B. Gamma knife radiosurgery for craniopharyngiomas : long term results in the first Swedish patients. J Neurosurg 2002 ; 97 (Suppl 5) : 613-22.

44 Jackson ASN, St George EJ, Hayward RJ, Plowman PN. Stereotactic Radiosurgery VIII. Recurrent intrasellar craniopharyngioma; Br J Neurosurg 2003; 17:18-43.

45 Solanki GA., Phipps K, Saunders D, Harkness W, Thompson D, Hayward RD. Optimum frequency and duration of childhood surveillance imaging in attempted curative treatment of craniopharyngioma. Childs Nerv Syst 2004; 20: 659.

46 Pan DH, Lee LS, Huang CI, Wong TT. Stereotactic internal irradiation for cystic craniopharyngioma: a 6-year experience. Stereotact Funct Neurosurg 1990; 54: 525-30.

47 Bremer AM, Nguyen TQ, Balsys R. Therapeutic benefits of combination chemotherapy with vincristine, BCNU and procarbazine on recurrent cystic craniopharyngioma. J Neurooncol 1984; 2: 47-51.

48 Lippens RJJ Rotteveel JJ, Otten BJ, Merx H. Chemotherapy with adriamycin (doxorubicin) and CCNU (lomustine) in four children with recurrent craniopharyngioma. Eur J Pediatr Neurol 1998; 2: 263-8.

CHAPTER ONE

Appendix 1

Post-Operative Fluid Management Guidelines and Nursing Charts for Management of Pituitary and Suprasellar Tumours.

1. Background

In inpatient post surgical settings, a classical tri-phasic response in anti diuretic hormone (ADH) secretion can occur.

i. An initial phase of diabetes insipidus (DI) due to oedema, manifesting within 24 post-operative hours and lasting up to 2 days.

ii. A second subsequent phase of either normal fluid regulation or of inappropriate ADH secretion (SIADH) lasting 1-14 days. The latter is presumed to be due to vaso-pressin neuronal necrosis.

iii. A third phase of permanent DI can follow, especially after severe and prolonged SIADH.

The above three phases may each also occur independently.

Patients with DI at presentation may require larger desmopressin doses post-operatively.

Cerebral Salt Wasting (CSW) due to over secretion of atrial or brain natriuretic peptide (ANP) causing natriuresis and diuresis, can also develop as a primary or as a secondary response to SIADH (directly via ADH or through plasma volume expansion).

2. Post-operative Management

The following are essential monitoring:

- accurate 6-8 hourly fluid balance, inserting a urinary catheter if necessary.
- where catheterised, hourly urinary output and specific gravity; otherwise specific gravity on all urine samples
- immediately postoperative and 8 hourly paired plasma and urine osmolality, electrolytes and glucose. changes in plasma sodium >5 mmol/L require more frequent measurements (4-6 hourly).
- daily weight, at 08.00-09.00 am before breakfast as soon as feasible

Thirst: Establish whether there is thirst impairment once the patient regains consciousness.

Appendix 1

Initial Recommended Management: Euvolaemic State

a.

If plasma sodium is between 132-150 mmol/L with normal osmolality:

- **Fluid maintenance** *(euvolemic status, table 1)***:** Maintenance fluid rates with 0.45% saline / 5% dextrose should initially be commenced, aiming for a daily positive fluid balance to allow for insensible losses, of 300mls/m^2/day. Fluid losses in excess of the maintenance fluid rates **minus** 300ml/m^2/day, should be replaced volume for volume by calculating and matching fluid balance at least 6 hourly (in arrears). A change to oral route should be encouraged as soon as tolerated.

- Fluid retention in excess of 300mls/m^2/day (anuria or oliguria) should result in an according decrease in fluid input rates balanced volume for volume with urine output ie. in 24 hour period

Fluid input = urine output + 300mls/m^2/day insensible loss.

- Enteric and CSF losses require replacement with normal saline (0.9%) volume for volume. Fluctuations in plasma sodium concentration of > 12mmol/day (or > 6 mmol/12 hours) should be avoided.

Table 1: Daily fluid maintenance (Euvolaemic Status)

Body weight	Fluid maintenance (mls/kg/hr)	eg. for a child of SA 1.0m^2: 10 X 4 = 40 mls 10 X 2 = 20 mls 10 X 1 = 10 mls Total input =70 mls/hr = 1680 mls/day Ideal output=57mls/hr=1680-300mls = 1380mls/day Hence replace hourly urinary losses in excess of 57 ml/hr fluid restrict if fluid retention in excess of 57ml/hr
First 10 kg	4	
Second 10 kg	2	
Subsequent kg	1	

Appendix 1

Management of Hypernatraemia: *(Algorithm 1)*

b.

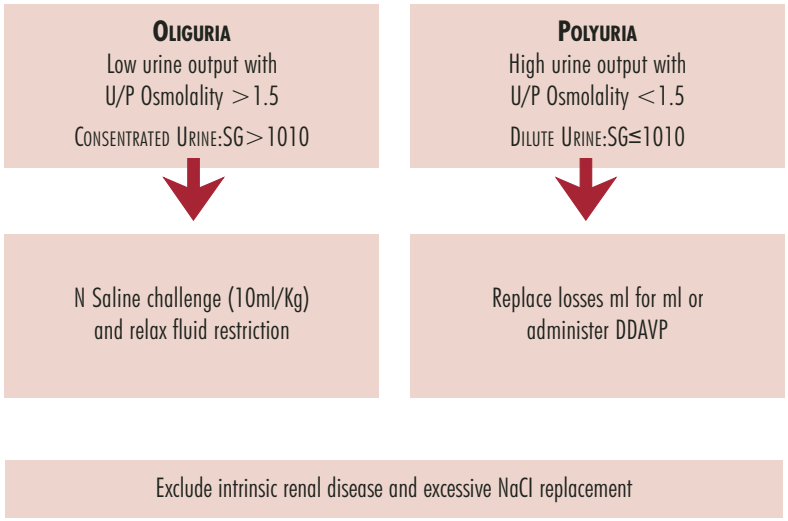
If normo-glycaemic, plasma sodium >150 mmol/L and plasma osmolality >300 mosmol/l

- Assess patient for hypo-volemia. If urine output is <1ml/kg/hr, urine/plasma osmolality ratio >1.5, or hourly urinary specific gravity >1010, consider 0.9% saline challenge (10ml/kg) and an appropriate increase in fluid intake. Maintain a more concentrated infusion solution (ie 0.45% or 0.9% saline) to avoid precipitous changes in plasma sodium concentration.

- If urine output is >4-5 mls/kg/hour for at least 2 consecutive hours, and urine/plasma osmolality ratio <1, or hourly urinary specific gravity ≤1010, increase fluid intake to match any accruing deficit, or administer a stat dose of desmopressin (DDAVP) *(see DI session on next page)* and observe urinary output carefully.

Algorithm 1

Management of Hypernatraemia



Appendix 1

Management of Hyponatraemia *(Algorithm 2)*

c.

-

-

-

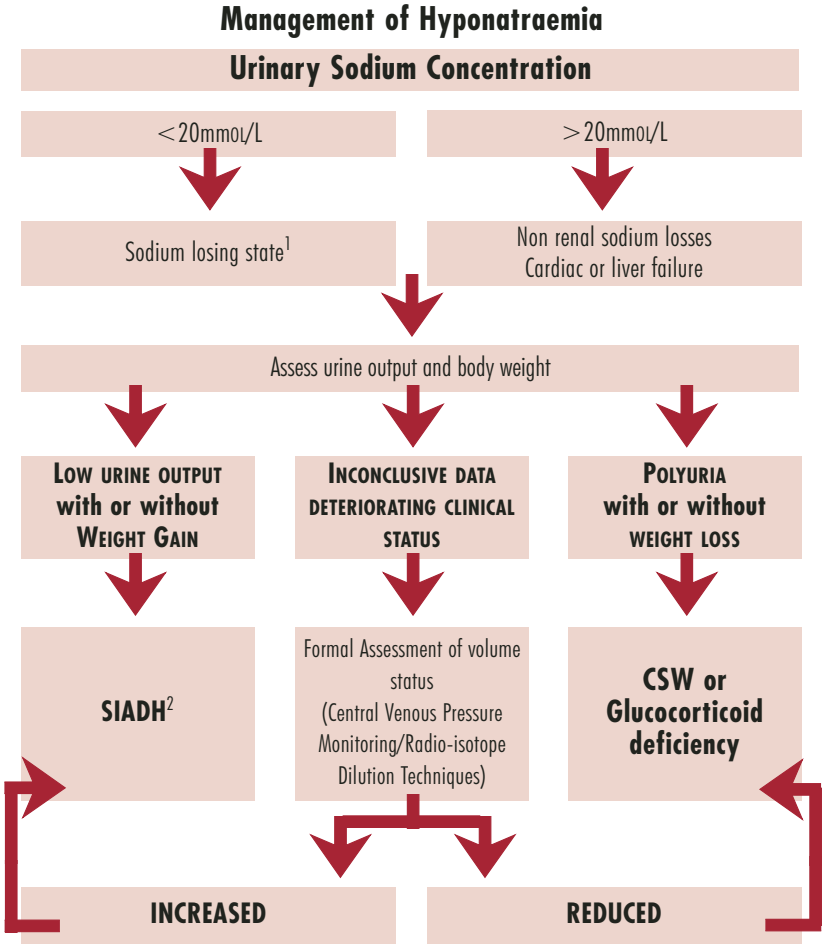
If plasma sodium is<132 mmol/l and osmolality <270 mosmol/l

If this occurs with urine/plasma osmolality ratio >1.5, hourly urinary specific gravity >1010 and low to normal urine output (urinary sodium > 20 mmol/l in a timed volume of urine), consider a diagnosis of SIADH. Restrict fluid intake and monitor progress *(see SIADH section below)*. In the absence of improvement or the development of polyuria, consider a diagnosis of CSW. Treatment will be based on sodium chloride (NaC1) and fluid replacement *(see CSW section below)*.

It is important to ensure adequate cortisol and thyroid replacement and exclude contributory renal or iatrogenic pathologies (ie diuretics and anti-epileptic medications).

Due to the risk of pontine myelinolysis following precipitous correction of hyponatremia, only symptomatic severe hyponatremia, (seizures and/or coma), justifies partial correction by hyper-osmolar saline infusion, i.e. 3% NaCl (500 mmol/1) at 1-2 ml/kg/hour, 0.5-1 mmol/kg/hour, for 2 to 3 hours) followed by conservative measures to limit the rate of correction to less than 12 mmol/l per day. The infusion rate should deliver a correction of plasma sodium concentration of 0.5 mmol/l/hr up to 125 mmol/l and then full normalisation over the next 2 days.

Algorithm 2



1: Exclude use of diuretics and intrinsic renal disease
2: Exclude antiepileptic induced SIADH

CHAPTER ONE

Appendix 1 Management of Specific Conditions

a. Diabetes Insipidus (DI):

Intra-operative fluid overload with subsequent hypo-osmolar polyuria may masquerade as DI in the early postoperative period.

The diagnosis of DI is made when plasma hyper-osmolality (>300 mosmol/L) coexists with urine hypo-osmolality (urine/plasma osmolality ratio <1) and polyuria (> 4-5 ml/kg/hr for 2 consecutive hours + urine SG < 1.010). If access to fluid is restricted (i.e. patients who are adipsic, unconscious or nil by mouth), severe hypernatraemia can develop quickly.

The initial phase of confirmed DI in a euvolaemic child commenced on maintenance fluids could either be managed by replacement of fluid losses volume for volume, or the careful administration of desmopressin. Low dose desmopressin should be used initially (5-10 microgrammes intranasally or 50-100 microgrammes orally or 0.1-0.2 microgrammes sc/im), and adjusted according to clinical response. Each subsequent dose should be administered after the demonstration of a dilute polyuria. Alternative regimens have included the use of dose-titrated continuous vasopressin infusions, but there is little justification for this approach as the vasopressin is virtually biologically inactive when administered in this way (it must be given within 15 minutes).

Regular desmopressin should only be prescribed when DI is stable and permanent. Desmopressin, rather than vasopressin, is the drug of choice due its longer duration of action and lack of vasoconstriction. The aim of treatment is attainment of an age- and weight- appropriate 24 hour urine output, with once daily pre-dose breakthrough polyuria to avoid water intoxication. In adipsic patients, a fixed daily fluid intake appropriate for weight and target weight, at which the patient is known to be eunatraemic and euvolaemic, should be established. Desmopressin dose is adjusted accordingly.

b. Syndrome of Inappropriate Antidiuretic Hormone (SIADH):

This condition is biochemically characterised by low plasma osmolality with inappropriately high urine osmolality (urine to plasma osmolality ratio >1.5, urine specific gravity >1010), hyponatremia with urine sodium loss >20 mmol/l, suppressed plasma renin activity, low haematocrit, low plasma urea and uric acid.

In the post-operative neurosurgical period, transient SIADH can be isolated or occur after an initial phase of transient DI. In the latter case, the reduction in urine output of increased urine osmolality, with increase in thirst (when intact) herald the fall in plasma sodium, characteristic of SIADH. Changes in body weight may be less sensitive.

Therapeutic intervention is fluid restriction. Sodium requires replacement only in prolonged SIADH causing total body sodium depletion. In severe hyponatremia diuretics or osmotic diuretics can be attempted.

c.

Cerebral Salt Wasting (CSW):

This condition is biochemically characterised by a low plasma osmolality with inappropriate high urine osmolality (urine to plasma osmolality ratio >1, urine specific gravity >1010), hyponatremia with natriuresis (urinary sodium losses up to 10-20 times normal), normal/high haematocrit, and plasma urea. Plasma renin activity may be high-normal or frankly elevated; occasionally it is depressed or normal. By contrast to SIADH *(Table 2)*, there is polyuria with a net negative water and sodium balance and clinical evidence of volume depletion (i.e. hypotension). Severe dehydration will reduce the polyuria which can be unmasked by saline challenge.

Treatment of CSW requires aggressive replacement of urine salt and water losses. In some patients mineralocorticoid supplementation (9α fludrocortisone) can also be helpful.

In patients in whom DI and CSW coexist, natriuresis in itself contributes to the polyuria. The latter should not be considered a sole index of poorly controlled DI. Higher desmopressin doses increase renal free water re-absorption and aggravate hyponatremia and should be avoided. Treatment consists of sodium and fluid replacement titrated against losses and cautious continuation of desmopressin, with close monitoring of plasma electrolytes and osmolality. Central venous pressure monitoring becomes mandatory to guide fluid replacement in deteriorating patients.

Table 2: Differential Diagnosis between SIADH and CSW.

	SIADH	CSW
Plasma volume	High	Low
Evidence of volume depletion	No	Yes
Plasma sodium	Low	Low
Urine sodium	High	High
Net sodium loss	Normal	Very High
Urine output	Usually Low	Very High
Serum Uric acid	Low	Normal
Plasma renin	Suppressed	Normal/High/Suppressed
Plasma aldosterone	Normal/High	Suppressed
Plasma ADH	High	Suppressed
Plasma ANH	High	High

The most important factors are highlighted in red.

CHAPTER ONE

Appendix 1

Steroid Maintenance Therapy

When dexamethasone dose is reduced to less than 1 mg/day, start hydrocortisone, at a maintenance dose of 10-12 mg/m^2/day. This is given in two or three divided doses: $^{2}/_{3}^{rd}$ am, $^{1}/_{3}^{rd}$ pm if twice daily administration, or $^{2}/_{4}^{th}$ am, $^{1}/_{4}^{th}$ early afternoon and $^{1}/_{4}^{th}$ early evening if thrice daily administration.

Hydrocortisone tablets should be used in preference to solutions which are notoriously prone to forming suspensions and hence unreliable. If necessary tablets may be crushed and taken with food.

In acute, severe illness/trauma the combination of hypo-cortisolism and DI is potentially lethal, particularly if combined with adipsia. Cortisol is required for the excretion of free water in the renal tubule and its relative deficiency can lead to water intoxication. Consequently in acute illness, the desmopressin dose should be withheld until dilutional hyponatremia is excluded and/or polyuria supervenes and hydrocortisone stress doses are being administered.

Prior to discharge, it is mandatory for patients/families to have been educated in emergency hydrocortisone procedures, to be aware of the potential for hypoglycaemia and hyponatremia during intercurrent illness as well as the need to double or triple the maintenance hydrocortisone dose whilst withholding desmopressin as above and seeking urgent medical attention during such crises. Patients should carry a steroid card and Medic Alert bracelet/necklace.

Thyroxine:
If there is biochemical evidence of secondary hypothyroidism (low serum $FT_4 \pm FT_3$ with low/normal serum (TSH), thyroxine replacement should be commenced (25-50 micrograms/day). Adjustments to the thyroxine dose require titration against the serum FT_4 and (occasionally) FT_3 level, which should be kept in the upper third of the reference range.

Follow-Up

Anterior pituitary function needs to be formally tested in all patients at a time determined by the paediatric endocrinologist. Until then the patient should be considered cortisol deficient and maintained on hydrocortisone replacement according to local guidelines

Appendix 1

Endocrine Fluid Balance Flow Chart For DI, CSW and SIADH

IMMEDIATE POST OPERATIVE MANAGEMENT:

- **Assess volume status -** Cardiovascular observations, perfusion, oedema, fluid balance, paired urine and plasma U&E's, glucose and osmolalities, urine SG and urine output. If volume depleted consider 10ml/kg fluid challenge (NaCl 0.9%). Fluid restrict if oedematous.
- **Fluids -** IV 0.45% NaCl & 5% Dextrose or oral fluids if tolerated.

  Insensible losses - 300mls/m^2/24hrs

  Maintenance fluid - 4ml/kg/hr - first 10kg, 2ml/kg/hr - second 10kg, 1ml/kg/hr for each subsequent kg.
- Maintain neutral fluid balance **plus** insensible losses **(i.e. Input = Output plus 300mls/m^2/24hrs)**.

EUVOLAEMIC STATE :
Plasma Na^+ 132 - 150mmol/L

Stable biochemistry and urine output
AND
Neutral fluid balance

(Input = output PLUS 300mls/m^2/ 24 hrs)

Continue with management plan
AND
Replace any accruing negative balance in arrears.

Check paired U&E's glucose & osmolalities BD (lab) with iSTAT Na^+ if required.

Assess daily cumulative balance and daily weight (when feasible)

DAILY ENDOCRINE REVIEW REQUIRED

HYPERNATRAEMIC STATE:
Plasma Na^+ >150mmol/l
Plasma osmolality > 300

CONCENTRATED OLIGURIA
Urine output <1ml/kg/hr
Urine/plasma osmo ratio >1.5
Urine SG >1.010

Fluid challenge 10mls/kg NaCl 0.9% and consider increasing fluid intake.

DILUTE POLYURIA
Urine output > 5ml/kg/hr for 2 consecutive hours
AND
Urine/plasma ratio <1
Urine SG < 1.010

Increase fluid input by continuing maintenance and insensible losses
AND
Replacing any accruing negative balance ml/ml in arrears.
OR
Give one dose of DDAVP. (50 - 100mcg oral/ 0.1 - 0.2mcg sc/im)
MUST DISCUSS WITH ENDOCRINE TEAM

Aim to keep daily cumulative balance within ± 3% of bodyweight.
If fluid balance more than 3% of body weight positive or negative, inform endocrine team.

HYPONATRAEMIC STATE:
Plasma Na^+ <132mmol/l
Plasma osmolality <270

Check urine Na^+, glucose, SG.
Assess urine output, body weight (if possible), assess fluid balance and volume status.

CONCENTRATED OLIGURIA

Urine glucose negative
Urine Na^+ 20 - 50 mmol/l
Urine/plasma osmo ratio >1.5
Urine SG>1.010
± weight **gain**

S.I.A.D.H
Fluid restrict
DISCUSS WITH ENDOCRINE TEAM

CONCENTRATED POLYURIA

Urine glucose negative
Urine Na^+ >70 mmol/l
Urine/plasma osmo ratio >1
Urine SG>1.010
± weight **loss**

C.S.W. or renal tubular leak.
Replace urine and Na^+ losses with NaCl 0.9% ml/ml
DISCUSS WITH ENDOCRINE TEAM

If these results are inconclusive i.e urine Na^+ <50mmol/l and clinical status deteriorating then seek urgent medical review.

Consider NaCl 0.9% bolus if possibility of volume depletion.

CHAPTER ONE

Appendix 1

Summary of Management of Specific Endocrine Conditions

NB ; THIS FLOW CHART AND SUMMARY ARE BASED ON, AND FOR USE IN CONJUCTION WITH, THE GUIDELINES ON PERIOPERATIVE FLUID BALANCE IN PATIENTS WITH CRANIOPHARYNGIOMA AND OTHER SUPRA/SELLAR-TUMOURS.

In inpatient postneurosurgical settings, a classical tri-phasic ADH secretion response occurs:

1. An initial phase of DI due to oedema, manifesting within 24hrs post op and lasting up to 48hrs.
2. A subsequent phase of either normal fluid regulation or of SIADH lasting 1 - 14 days.
3. A third phase of permanent DI can follow, especially after severe, prolonged SIADH.

The above three phases can also occur independently.
Patients with DI at presentation may require larger or smaller DDAVP doses post op.
CSW can also develop and/or co-exist with DI as a primary (neuronal insult) or secondary response to SIADH.

PRE-OPERATIVE MANAGEMENT:
Auxology - Height, weight, surface area, pubertal ratings and bone age.
Investigations - Paired plasma and urine osmolalities, glucose and U&E's, 08.00h plasma cortisol (if not on steroids), prolactin, (to rule out prolactinoma pre-op) AFP & βHCG (to rule out SGCT), thyroid function (FT4, TSH), IGF - 1 (baseline to assess future growth hormone deficiency. LH and FSH if >8yrs old

PRIOR KNOWLEDGE OF PAIRED URINE AND PLASMA ELECTROLYTES, OSMOLALITIES AND GLUCOSE AND LIASON WITH THE ENDOCRINOLOGIST AND ANESTHETIST ARE VITAL.
Steroid cover for surgery - If patient on dexamethasone no further steroid cover required. Otherwise, hydrocortisone - 2mg/kg IM/IV - should be given on induction of anaesthetic. Operations over 4 hours will require further bolus of hydrocortisone. It should be noted that ACTH deficiency may conceal DI and cortisol replacement unmask it.
DDAVP - Patients with DI pre-op should have their DDAVP pre surgery.

POST - OPERATIVE MANAGEMENT :
Accurate 6 -8 hourly fluid input and urine output with urine specific gravity and glucose dipstix on all early morning urine samples or, when catheterised, these biochemical parameters should be assessed hourly.
Immediate post-op and 8 -12 hourly paired plasma and urine osmolarities, U&E's and glucose. Precipitous changes in plasma Na^+ will require more frequent measurement (4 - 6 hourly).
Daily weight before breakfast (09.00h) as soon as feasible.
Establish whether there is thirst impairment once the patient is conscious.

DIABETES INSIPIDUS.
Intraoperative fluid overload with subsequent hypo-osmolar polyuria can masquerade as DI in the early post-op period.

The diagnosis of DI is made when plasma hyper-osmolality (>300mosmol/l) coexists with urine hypo-osmolality (usually <300mosmol/l) (urine/plasma osmolality ratio <1), polyuria (>5 ml/kg/hr for 2 consecutive hours), which is dilute, urine SG <1.010, and hypernatraemia. If access to fluid is restricted (i.e. patient is adipsic, unconscious or NBM), severe hypernatraemia and dehydration can develop quickly with a secondary paradoxical oliguria/anuria. If polyuria is severe, urinary salt losses also follow (20-70mmol/l).

The initial phase of confirmed DI can either be managed by replacement of fluid losses volume for volume OR the careful administration of DDAVP (see flow chart). Low dose DDAVP should be used initially (50 - 100μg orally or 0.1 - 0.2μg sc/im) and adjusted according to clinical response. Each subsequent dose should be administered after demonstration of a **dilute** polyuria. Regular DDAVP should only be prescribed when DI is stable and permanent. The aim of treatment is attainment of an age and weight appropriate 24 hour urine output, with once daily pre-dose breakthrough polyuria to avoid water intoxication. In adipsic patients, a fixed daily fluid intake appropriate for weight and target weight, at which the patient is known to be eunatraemic and euvolaemic, should be established. DDAVP dose adjusted accordingly to achieve this.

S.I.A.D.H.
This condition is biochemically characterised by low plasma osmolality with inappropriately high urine osmolality (urine/plasma osmolality ratio >1.5), a concentrated oliguria (<1 ml/kg/h) urine SG >1.010, hyponatraemia, urine Na^+ loss between 20mmol/l-50mmol/l, suppressed plasma renin activity, low haematocrit, low plasma urea and uric acid.

In the post-op neurosurgical period, transient SIADH can be isolated or occur after an initial phase of transient DI. In the latter case, the reduction of urine output, increased urine osmolality, with increase in thirst (when intact) herald the fall of plasma Na^+, characteristic of SIADH. Changes in body weight may be less sensitive. Therapeutic intervention is fluid restriction. Na^+ requires replacement only in prolonged SIADH. It needs to be differentiated from other causes of post-op hyponatraemia (eg CSW)

CEREBRAL SALT WASTING.
This condition is biochemically characterised by a low plasma osmolality with inappropriately high urine osmolarity (urine/plasma osmolarity ratio >1), a concentrated polyuria (>5ml/kg/hr) urine SG >1.010, hyponatraemia with natriuresis (urine Na^+ 10 - 20 times normal), usually >140mmol/l), high hematocrit and plasma urea. By contrast to SIADH there is polyuria with a net negative Na^+ and water balance and clinical evidence of volume depletion. Severe dehydration will reduce the polyuria which can be unmasked by saline challenge.

Treatment of CSW requires aggressive replacement of urine salt and water losses. In patients in whom DI and CSW coexist, natriuresis contributes to the polyuria, the latter should not be considered a sole index of poorly controlled DI. Higher DDAVP doses can aggravate hyponatraemia and should be avoided. Treatment consists of sodium and fluid replacement and cautious continuation of DDAVP, with close monitoring of fluid, electrolytes and osmolality. Renal tubular dysfunction and diuretics are other causes of urinary salt loss which require consideration. Anticonvulsants also affect renal excretion of water.

Appendix 1

Fluid Monitoring Chart for DI/SIADH/CSWS for bedside use

NAME:
HOSP NO:
DOB:

DATE									
TIME	AM	PM	24HR	AM	PM	24HR	AM	PM	24HR
PLASMA(pre DDAVP)									
Na^+ (mmol/l)									
K^+ (mmol/l)									
Urea									
Creatinine									
PO^4 (mmol/l)									
Ca^+ (mmol/l)									
Glucose (mmol/l)									
Osmolality(mmol/kg)									
URINE									
Osmolality(mmol/kg)									
S.G.									
Na^+ (mmol/l)									
Glucose (mmol/l)									
U/O (mls/kg/hr)									
Total volume (mls)									
FLUIDS (IV/PO)									
Maintenance									
(mls/kg/day)									
Fluid type									
Rate (ml/kg/hr)									
Total volume (mls)									
Total Na^+ in **(mmol)**									
MEDICINES									
DDAVP SC/PO/Nasal									
Hydrocortisone PO/IV									
Dexamethasone PO/IV Other Meds **eg**									
Fludrocortisone μg, anti convulsants etc									
WEIGHT									
Kg									
BALANCE (±)									
12 hrly - mls									
BALANCE (±)									
Cumulative - mls									
PLAN									

RENIN:	ALDOSTERONE:	DATE:
ADMISSION WEIGHT:	LAST CLINIC WEIGHT (EUVOLAEMIC/EUNATRAEMIC):	

CHAPTER TWO

Chapter 2 - Adrenocortical Tumours (ACT)

2.1 Executive Summary

Main issues

Adrenocortical tumours (ACT) are rare in childhood often occurring in genetically susceptible individuals, and may present atypically or with complex adrenal steroid hypersecretion. The diagnosis should always be considered in the child with refractory hypertension.

The management of these heterogeneous ACT requires complex multidisciplinary expertise.

Their accurate diagnosis relies on early and detailed endocrine biochemistry to exclude more common adrenal biosynthetic disorders and guide appropriate endocrine management.

Histology is not a reliable prognostic indicator; tumour size, weight and extent of surgical resection are more predictive.

The dismal outcome for patients with unresectable residual disease uncontrolled by adrenotoxic agents, has led to the need for mandatory trials of systemic chemotherapy. The efficacy of radiation therapy has not been established and should be approached with caution given the prevalence of p53 germline mutations. It may merit consideration, however in selected individual situations.

Long term endocrine follow-up with detailed endocrine biochemistry and growth and developmental review is mandatory.

Continuing endocrine (as well as oncological) data collection is important for increasing understanding of this rare disorder.

Main recommendations

Early and adequate endocrine biochemistry is necessary for characterising the tumour and directing appropriate specific treatment of any endocrine complication (eg hypertension).

X-Ray irradiation should be kept to a minimum given the high prevalence of p53 germline mutations and risk of second tumours.

Abdominal ultrasound should be the first line of radiological investigation in suspected ACT; a normal scan does not exclude the diagnosis.

Pre-operative CT/MRI of the abdomen is mandatory for surgical planning. Chest CT and further staging procedures are indicated by the finding of large, potentially malignant adrenal masses. Pre- and peri- operative medical management and antihypertensive therapy should be undertaken in consultation with a paediatric endocrinologist.

Surgery should be undertaken in a tertiary UKCCSG-affiliated endocrine centre by an experienced surgeon recommended by the multidisciplinary team (MDT), with the aim of complete tumour resection including sites of metastatic disease where possible.

Post operative endocrine management can be complex requiring glucocorticoid supplementation at stress doses and/or pressor support.

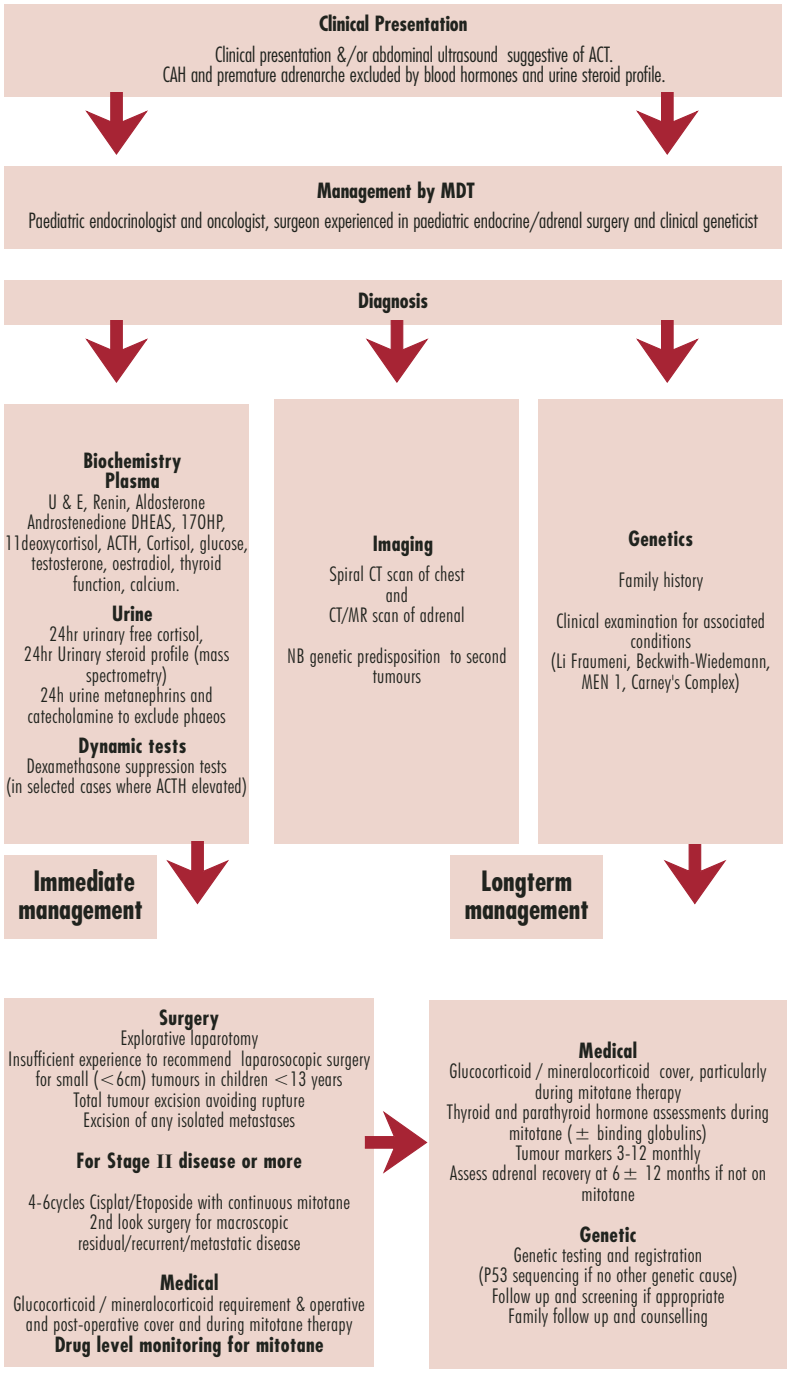
In functioning tumours, assessment of post-operative residual disease is best undertaken by steroid tumour markers.

Subsequent adjuvant therapy is determined by a staging system based on tumour volume and extent of residual disease.

Hormone replacement therapy maybe required for many months until recovery of contra-lateral adrenal function; ongoing endocrine review should continue 3-6 monthly until adulthood and then lifelong.

Genetic referral and investigation must be offered and long-term follow-up for second tumours recommended.

Adrenocortical Tumours (ACT) Management Pathway



CHAPTER TWO

2.2 Introduction and UK Registry Data

Adrenocortical tumours occur very rarely in childhood, more often in girls than boys (2:1) [1]. Peak childhood incidence is at 3.5 years of age.

When they occur they are frequently (80-90%) associated with complex, disordered hyper- and/or hypo-function of the adrenal gland and clinical features consequent on hormone (usually androgen) excess[2,3,4]. ACT are often inefficient at producing cortisol, tumour activity being dominated by secretion of androgens and, less commonly, intermediates such as 11-deoxycortisol and 11-deoxycorticosterone. Glucocorticoid excess (Cushing's syndrome) can also occur, usually but not exclusively in combination with androgen excess.

The distinction between adenoma and carcinoma is difficult and has historically relied upon tumour size and imaging, or histopathological evidence of local invasion or metastases. Smaller tumours (<200cm^3 or <100g) are more easily completely resected and so more usually cured. Larger tumours are less likely to be resected.

Older patient age, tumours larger than 100g (or 200cm^3) and peri-operative tumour spillage/dissemination are poor prognostic factors for ultimate cure.

Adrenocortical Tumours in National Registry of Childhood Tumours 1971-2000.

Table 1. Number of UK registrations of Adrenocortical Adenomas by Age and Sex (1991-2000)

	0-4years	5-9years	10-14years	Total
Male	3	1	0	4
Female	5	5	2	12
Total	8	6	2	16

Current UK registration of adrenocortical adenomas is almost certainly incomplete (29 between 1971 and 2000, of which 16 since 1991) and hence understanding of their behaviour and outcome is limited.

Table 2. Number of UK Registrations of Adrenocortical Carcinoma by Age and Sex (1971-2000)

	0-4years	5-9years	10-14years	Total
Male	12	2	3	17
Female	31	12	11	54
Total	43	14	14	71

Adrenocortical Carcinomas (ACC) are exceptionally rare childhood malignancies with a global, likely underestimated, incidence of 0.5 in a million and a very poor prognosis -(5 year actuarial survival 36 %). Deaths beyond 5 years occur, most frequently due to second malignancies (UK National Registry).

Adreno-cortical carcinoma (ACC) may be a manifestation of a genetic disorder (e.g. Li-Fraumeni, Beckwith-Wiedemann)

Primary hyperaldosteronism (Conn's syndrome) is an extremely rare ACT[5] in childhood and is not discussed within the remit of this document.

2.3 Presentation (Functioning and non-Functioning) Tumours

ACT may present with the following features:

- syndromes of hormone excess,
  - childhood virilisation not caused by congenital adrenal hyperplasia (CAH) or premature adrenarche in 80-90% cases. Acne in a child under 6 years should make the exclusion of ACT a priority.
  - Cushing's syndrome in a third of cases, with associated physical changes and growth failure [2,3,4]. This may co-exist with androgen excess.
  - hypertension is often present; children may rarely present in hypertensive crisis[(2,3,4)],
- abdominal mass,
- clinical screening of an individual known to be at genetic risk.

2.4 Statement of Best Practice

Once the diagnoses of adrenarche, true precocious puberty and congenital adrenal hyperplasia (CAH) have been excluded by appropriate blood tests and urinary steroid profile analysis, the patient should be referred to a tertiary endocrine and UKCCSG centre. To secure a diagnosis, and because of the rarity and potential complications of this disease, it is important that the child is managed by a specialist paediatric endocrine team (with access to adult endocrine specialists), in conjunction with a paediatric oncologist and a surgeon experienced in paediatric adrenal tumour surgery.

Successful surgical management is dependent upon appropriate surgical expertise, expert pre-operative therapeutic stabilisation and skilled anaesthetic care, particularly for functioning adrenal tumours. The child should be scheduled for early surgery.

2.5 Pre-Operative Diagnostic Investigations

i. Biochemistry

Secreting Tumours

The following tests should be performed in any virilised child with a suspected adrenal tumour in whom more common causes (CAH, adrenarche) have been excluded:

- serum electrolytes, cortisol, dehydroepiandrosterone sulphate (DHEA-S), testosterone, androstenedione (A^4), oestradiol, renin, aldosterone, 17-hydroxy progesterone and 11-deoxycortisol (to assess normal and abnormal hormone production)
- serum glucose (to exclude secondary glucose intolerance from glucocorticoid excess)
- serum FT_4, TSH, calcium (as a baseline for future targeted medical therapy)
- 24h urine metanephrines and catecholamines to exclude phaeochromocytoma *(see guideline on phaeochromocytoma.)*
- 24h urine for steroid profile, characteristic for functioning ACT [6]. Urine steroid profile analysis can exclude adrenarche and congenital adrenal hyperplasia (CAH) more accurately than serum[7], and provides a tumour marker for monitoring therapeutic response and detection of tumour relapse.
- 24h Urine free Cortisol (UFC) or serum cortisol profile, to exclude co-existing subclinical glucocorticoid excess.
- 24.00h and 08.00-09.00h measurement of plasma cortisol and Adrenocorticotrophic hormone (ACTH) to separate ACTH-dependent Cushing's disease from glucocorticoid secreting ACT (suppressed 0800 - 09.00h ACTH).
- overnight (0.3mg/m^2) low and high (0.5mg and 2mg 6hrly for 48h respectively) dose dexamethasone suppression tests may need to be performed (dose-adjustments according to local protocols) to investigate glucocorticoid excess syndromes. These will not suppress the output of abnormal steroids in the case of functioning ACT.

NB The 24h urine collection for a steroid profile should be commenced after the third dose (i.e. during the second 24h) and plasma for cortisol and DHEAS, ACTH taken at 0800h after the 4th dose (i.e. 48h after start)

Non-secreting Tumours

Malignant ACT may rarely (10%) be non-functioning.

The differential diagnosis of a **non-secreting** adrenal mass includes neuroblastoma; further investigation of such a tumour should therefore include measurement of 24h urine catecholamines and follow current UKCCSG neuroblastoma management guidelines.

ii. Imaging

Exposure to repeated X-ray radiation for diagnosis and subsequent follow-up should receive cautious consideration in view of the likely genetic predisposition and propensity to second tumours.[8]

Imaging of the chest by spiral CT should be obtained at baseline in all cases of ACT because of the potential for metastases even with small tumours. It is particularly important in the 10% of tumours which are non-functioning and in whom there are no biochemical markers of disease.

Abdominal ultrasound should be the first line of radiological investigation in suspected ACT but may be difficult in larger or obese patients. It is the optimum technique to assess for caval extension of tumour thrombus.

Where abdominal ultrasound is negative but suspicion of ACT persists, MRI or CT is recommended. MRI is preferred as it lacks ionising radiation.

CT or MRI of abdomen is also mandatory for surgical planning. Pre-operatively MRI gives a better definition of tumour extent and invasion into adjacent structures.

Under no circumstances should scan directed or open biopsy be performed because of the risk of tumour seeding.

2.6 Pre-operative Medical Management/Preparation for Surgery

Pre-operative anti-hypertensive therapy may be necessary and should be undertaken according to local protocols and in consultation with a paediatric endocrinologist. Hypertension, particularly that resulting from steroid excess, may be refractory to conventional agents or vasodilators and require specific therapy with metyrapone (an 11β hydroxylase inhibitor), ketoconazole, or mitotane, targeted at blocking single or multiple enzymatic steps in steroid biosynthesis although therapeutic levels of mitotane may only be reached after several months. Spironolactone, an aldosterone antagonist, in large doses may be quicker in action and be additionally required in cases of refractory or malignant hypertension.

Plasma cortisol, electrolytes and blood glucose should be determined and any appropriate corrective treatment commenced. Some patients may benefit from pre-operative normalisation of cortisol excess and steroid biosynthetic blockade may again be necessary.

All families should have informed discussion of possible success and failure rates and possible short- and long-term complications with the various procedures.

2.7 Operative Management

Surgery should be considered in all cases of childhood ACT. Inoperable tumours and macroscopic residual disease have dismal prognoses.

For childhood ACT with a significant probability of malignancy, laparoscopic removal is not currently recommended as the long term outcome is unclear[9]. The standard approach to resection is via an open, transperitoneal route.

In highly experienced hands and in older (>13 years) patients with a low probability of malignancy (eg in Beckwith-Wiedemann syndrome), removal of small tumours (<6 cm) by a transperitoneal or retroperitoneal route might be carefully considered[9].

The surgical approach to large, potentially malignant, tumours will be influenced by the surgeon's experience.

Complete, radical surgical resection of tumours is the treatment of choice and can be curative even for malignant tumours, especially in small tumours. Patients achieving complete resection survive significantly longer than those with residual disease[2,10].

Peri-operative rupture of ACT is a poor prognostic factor and should be avoided where possible [11].

Open surgical resection should be preceded by full laparotomy, including inspection of the contralateral adrenal. Biopsy of the apparently normal side is not routinely recommended.

In secreting, large (>200cm^3) potentially malignant tumours, resection should include any obvious lymph nodes, whether or not seemingly involved, on the affected side. The entire operative specimen should be transferred fresh and unsectioned (so that capsular invasion can be adequately assessed) directly to the pathology department. Use of formalin solution will render the specimen useless for biological studies, which are encouraged.

2.8 Peri-Operative Medical Management

Peri-operative hormonal therapy should be undertaken by the paediatric endocrinologist. Patients with pre-operative Cushing's syndrome and ACTH suppression will inevitably experience hypoadrenalism after successful tumour resection. These patients require intravenous cortisol at stress doses at the point of tumour removal and subsequently in appropriate weaning doses over time, until normal adrenal function is established.

Patients with severe or malignant hypertension pre-operatively are at risk of sudden hypotension with successful surgery. Temporary pressor support may be required on tumour removal, and in the subsequent immediate post-operative period.

2.9 Histopathology, Staging and Prognostic Factors

The histopathological distinction between adrenal adenoma and carcinoma is difficult. It is widely accepted that tumour size is the best available predictor of biological behaviour, tumours > 100g / 200 cm^3 being associated with worse prognosis[12].

Other poor prognostic factors include older age at presentation, increased urinary steroid DHEAS and glucocorticoid hormone levels, hypertension, peri-operative tumour rupture[9] and delay in diagnosis[3].

Capsular and vascular invasion has been associated with a high frequency of recurrence[2].

A modification of the Weiss criteria based on mitotic index, atypical mitoses, confluent necrosis and nuclear grade may also predict clinical outcome[13].

Staging

Stage	
I	Total excision of tumour, tumour volume < 200cm^3(100g) Absence of metastases and normal hormone levels after surgery
II	Microscopic, residual tumour, tumour volume >200cm^3, (100g) Persistently elevated adrenocortical hormone levels after surgery. *There are probably two sub-categories here:* IIA Children with resected tumours (>200cm3/100g) - 50% surgically cured IIB Patients with microsopic residual disease or persistent hormone excess - 100% progression.
III	Gross residual or inoperable tumour
IV	Distant metastases

In a recent series 78% had local disease (stage I & II), 9% had stage III disease and 13% had stage IV disease [2]

2.10 Post Operative Management

Perioperatively and immediately post-operatively, glucocorticoid supplementation **at stress doses** (and greater if mitotane, ketoconazole, or other adrenolytic drugs are used) will be required and gradually reduced to maintenance replacement on the advice of the paediatric endocrinologist according to local guidelines. In patients with ACTH suppression pre-operatively, contralatateral adrenal recovery may take many months or years.

Close observation (4-6hrly) of both mineralocorticoid (salt retention and hypertension) and plasma glucose is mandatory, as is awareness of potential for sepsis and hypotension in those who were cushingoid pre-operatively.

In the very rare event of a bilateral adrenalectomy, both glucocorticoid and mineralocorticoid replacement therapy will be required lifelong.

Assesment of residual disease should be undertaken according to whether the tumour is functioning or non-functioning.

i. **Functioning Tumours**

As a tumour marker, 24hr urine steroid profile should be checked early (at least one week) post-operatively. If there was evidence of glucocorticoid hypersecretion at diagnosis, this can be used as a tumour marker **only** if supportive glucocorticoid therapy has been withdrawn, **or** if dexamethasone is used as the replacement glucocorticoid.

Alternatively, 0800-09.00h serum cortisol levels taken the following morning, **provided** cortisol was the only steroid secreted in excess and hydrocortisone (or other glucocorticoids) have not been administered in the preceding 12hours.

ii. **Functioning and Non-Functioning Tumours**

If not performed pre-operatively, the following should now be undertaken:

- Spiral CT chest
- Isotopic bone scan is routinely recommended only in those with confirmed pulmonary spread (stage IV).

2.11 Medium to Longer Term Management

Since malignancy (excluding Conn's) cannot be excluded on histology, follow-up is mandatory. This should be lifelong to exclude contralateral or malignant recurrence. Patients with p53 germline mutations need a particularly close follow-up for the occurrence of other tumours.

i. **Stage** I

Complete resection, tumour <200cm^3/100g

Clinical and endocrine surveillance for signs and symptoms of steroid hormone excess should continue at least 3 monthly for the first year and at least 6 monthly for 5 years with the aim, after **unilateral** adrenalectomy, of withdrawing glucocorticoid (± mineralocorticoid) support; the contralateral adrenal gland may take up to 18 months or more to recover function.

If these were abnormal during initial assessment, 3-6 monthly measurements of blood pressure, blood and/or urinary steroid profiles are sensitive measures of recurrence, and more so than abdominal ultrasound.

3-6 monthly abdominal ultrasound should be used to screen for local recurrence of non-functioning tumours in particular, for at least the first two years.

ii. Stages II- IV

Incomplete resection, tumours >200cm^3 or metastatic disease

If not previously assessed for metastatic disease or there is biochemical evidence of residual disease, spiral CT chest (and isotopic bone scan in those with pulmonary disease, stage IV) are now indicated.

If there is no evidence of residual disease after removal of a tumour larger than 100g or 200cm^3, more frequent (3-monthly) clinical and endocrine review for signs and symptoms of increased steroid production is recommended, together with blood and urinary steroid profiles for functioning tumours, and abdominal ultrasound or MRI.

Treatment options include adjuvant chemotherapy and/or mitotane. Due to the rarity of this condition no randomised or controlled studies have been performed. An international registry of adrenocortical tumours is co-ordinated at St Judes' Hospital, USA, and recommends the use of mitotane with etoposide and cisplatinum chemotherapy (www.stjude.org/ipactr).

The efficacy of radiotherapy has not been established in children and should be used with caution in view of the genetic tumour susceptibility.

a. Endocrine replacement therapy

Post-operative medium to long term hypoadrenalism may result from contralateral adrenal suppression, (caused by initial Cushing's hypersecretion syndrome) or adrenotoxic therapy (eg mitotane) and requires endocrine supervision.

Starting doses of physiological glucocorticoid replacement therapy with dexamethasone (0.3mg/m^2/day in two divided doses) rather than either hydrocortisone (10-15mg/m^2/day in 2-3 divided doses) or prednisolone (3-4mg/m^2/day in 2-3 divided doses), have the advantage of not cross-reacting with the serum cortisol or 24h urine steroid profile which can thus be used to monitor tumour response. This benefit needs balancing against the possibility of avascular necrosis after dexamethasone, although the doses implicated are usually supraphysiological and cumulative. Larger (3-4 fold increase) glucocorticoid doses are required during mitotane therapy and/or during 'stress' periods and can be titrated against 08.00-09.00h ACTH measurements or UFC. Note that serum cortisol levels on mitotane are highly unreliable (it increases SHBG and metabolism of glucocorticoids). Mineralocorticoid replacement therapy (fludrocortisone) at once daily starting doses of 150µg/m^2 (and possible salt supplementation), can be titrated against measurements of plasma renin and electrolytes. Crushed tablets (rather than solutions/suspensions) of all steroid medications should be used to avoid degradation of the active substance.

b. **Mitotane**

Mitotane, the ortho-para derivative of an insecticide, dichlorodiphenyl-dichloroethane (DDD), was serendipitously noted to cause adrenal necrosis, leading to its use in malignant ACT [14].

Mitotane is usually effective in controlling the endocrine symptoms and may cause tumour regression, but is not a classical anti-neoplastic agent.

Although retrospective adult studies do not suggest mitotane influences survival [10], limited evidence suggests greater effectiveness in children [15-17], particularly if the neoplasm is hormonally active [18], and where therapeutic levels of 14-20 mg/l can be achieved without intolerable side effects [2, 19, 20].

Patients receiving mitotane should be carefully monitored for mineralocorticoid and glucocorticoid insufficiency and larger than normal replacement hormone doses may be necessary due to an increased serum steroid-binding capacity [19]. Serum thyroid and parathyroid gland function should also be carefully monitored (TSH, $FT_4 \pm FT_3$, calcium, PTH).

c. **Chemotherapy**

Effective chemotherapeutic agents include cisplatinum, etoposide, doxorubicin, 5-Fluoruracil and cyclophosphamide [2, 19, 21-27].

The combination of cisplatin, etoposide and mitotane, whilst tolerable, showed a survival advantage over chemotherapy alone in one adult study, but no randomised trials have been performed [19]. The latter are unlikely, even with international collaboration, given the rarity of malignant ACT in children.

d. **Radiotherapy**

Radiotherapy is not advised given the high chance of a genetic cancer predisposition.

Secondary tumours have been reported within the radiation field [28].

Radiation to the renal bed is contraindicated in the presence of a kidney (radiation nephritis)

e. **Second Look Surgery**

This should be attempted to resect macroscopic residual or metastatic disease *(see below)*

f. **Recommended Adjuvant Management Strategy for Stages II-IV**

Patients with malignant ACT at high risk of recurrence should receive cisplatin, etoposide and mitotane concurrently *(appendix 1 and 2)* and be re-assessed after 3 and 6 courses with an attempt at interim surgical resection of any residual disease.

Planned chemotherapy should be 6 courses, but may be extended in individual cases if the therapeutic indications outweigh toxicity.

Mitotane may need to be continued long term as tolerated; anecdotal experience suggests 18months to 2 years after remission may suffice, though some recommend longer.

It should be noted that adrenal recovery on mitotane discontinuation may not be complete.

2.12 Genetic Management

Since 50 to 80% of ACT's in childhood have an inherited basis, referral to the regional cancer genetics service is recommended.

50% of children with ACT have Li Fraumeni syndrome. ACT in childhood may be the first manifestation of Li Fraumeni syndrome within a family[29-31]. In addition 80% of sporadic childhood ACTs have atypical germline mutations of p53 associated with a lower but increased cancer risk in relatives[32, 33].

ACT can occur in patients with isolated hemi-hypertrophy and/or the Beckwith-Wiedemann syndrome [2,34].

ACT rarely occur in children with MEN 1 [35,36].

One third of patients with Cushing's syndrome have pigmented multinodular adrenocortical disease (PPNAD) of which The Carney Complex is a relatively common cause[37,38]. In these patients, however, the adrenals are usually functionally hyperactive but anatomically not enlarged or 'beaded'. Neonatal Cushing's syndrome should suggest McCune-Albright syndrome.

i. Family History

This should include at least 1st, 2nd and 3rd degree relatives, and a history of any benign or malignant tumours.

Li Fraumeni, MEN 1 *(see MEN 1 guideline)* or the Carney Complex may be diagnosable conditions from the family history.

ii. Clinical Examination for Associated Phenotypes

Beckwith Wiedemann - An overgrowth syndrome characterised by macroglossia, exomphalos, and organomegaly ± hemihypertrophy, with increased risks of Wilms and other childhood tumours, including ACT. Information about the risks, symptoms and signs of the associated tumours including ACT should be explained to parents.

The Carney Complex - An autosomal dominant susceptibility to cardiac myxomas associated with lentigines similar to those seen in Peutz Jeghers syndrome, cutaneous myxomas, psammomatous melanotic schwannomas, and pituitary and Sertoli cell tumours.

McCune-Albright - A mosaic syndrome due to Gsα mutations and associated with Cushing's syndrome due to adrenal nodular disease, polyostotic fibrous dysplasia and precocious puberty.

iii. Genetic Testing

This should be carried out at the regional centre where genetic counselling, family follow-up and genetic registration are available.

It should be offered for any condition diagnosed from the family history or clinical examination.

Families with the Carney Complex show genetic heterogeneity with linkage to 2p16 and 17q2. Mutations have been identified in the PRKAR1A in the 17q linked families [39].

Beckwith Wiedemann syndrome arises as a result of a number of different genetic mechanisms involving the 11p15 region.

The syndrome of MEN 1 is due to mutations in the MENIN gene.

p53 mutation analysis should be offered to all childhood patients with sporadic ACT where there is no known genetic disease (because of the high propensity to germline p53 mutations) and where Li Fraumeni is suspected. Sequencing of the entire gene is necessary[8].

2.13 Extended Surveillance

After completion of five-year cancer/tumour surveillance, the disease free child should remain under endocrine follow-up until adulthood, since pubertal progression may be disturbed by early endocrine events.

Female patients with residual cliteromegaly require endocrine and gynaecological follow-up, ideally in an age-appropriate multidisciplinary and specialised (intersex) setting with access to specialised intersex surgery and psychological support.

Genetic follow-up should continue throughout adulthood to ensure adequate counselling and surveillance for the individual and the family.

Patients with inoperable, relapsed and disseminated disease require multidisciplinary palliative support according to local UKCCSG guidelines together with endocrine liaison to adjust adrenotoxic therapy (to limit the effects of hormone excess syndromes) and symptomatic hormone support (to improve well-being and quality of life), in an appropriate risk-benefit equation guided by the individual needs of each patient.

2.14 Information and Support for Patients and Carers

Support groups are available through "Contact a family" directory for some genetic conditions with ACT.

Families may find useful information and contacts through www.cancerbacup.org.uk.

2.15 Registration and Tumour Banking

Patients with any ACT (benign or malignant) should be registered with the UKCCSG.

International registration **www.stjude.org/ipactr** to the International Paediatric Adrenocortical Tumour Register (IPATR), can be made at the same time and is recommended.

Consent for Tumour Banking according to the UKKCCSG protocol, is encouraged.

CHAPTER TWO

References

1. Stiller CA. International variations in the incidence of childhood carcinomas. Cancer Epidemiology, Biomarkers & Prevention 1984;3:305-310.
2. Teinturier C, Pauchard MS, Brugieres L, Landais P, Chaussain JL, Bougneres PF. Clinical and prognostic aspects of adrenocortical neoplasms in childhood. Med Ped Onc 1999;32:106-111.
3. Ribeiro RC, Sandrini R, Schell MJ, Lacerda L, Sambaio GA, Cat I. Adrenocortical carcinoma in children: A study of 40 cases. J Clin Onc 1990;8:67-74.
4. Sabbaga CC, Avilla SG, Schultz C, et ai. Adrenocortical carcinoma in children. J Pediatr Surg 1993;28:841-843.
5. Ribiero RC, Michalkiewicz EL, Figueiredo BD, de Lacerda L, Sandrini F, Pianovsky MD, Sampaio Grand, Sandrini R. Adrenocortical tumors in children. Braz J Biol Res 2000; 33: 841-3.
6. Wolthers OD, Cameron F, Scheimberg I, Honour JW, Hindmarsh PC, Savage MO, Stanhope RG Brook CGD. Adrenocortical tumours in children. Arch Dis Child, 1999, 80: 46-50.
7. Honour J.W., Price D.A., Grant D.B. Virilizing adrenocortical tumors in childhood. Pediatrics 1986 78: 547.
8. Varley JM, Mc Gowan G, Thorncroft M, James LA, Margison GP, Forster G, Evans DG, Harris M, Kelsey AM, and Birch JM. Are there Low-Penetrance TP53 Alleles? Evidence from Childhood Adrenocortical Tumors. Am J Hum Genet 1999;65:995-1006.
9. Cobb WS, Kercher KW, Sing RF, Henifrod BT Laparoscopic adrenalectomy for malignancy. Am J Surgery 2005; 189: 405-11.
10. Haak HR, Hermans J, Velde CJHvd, Lentjes EGWM, Goslings BM, Fleuren G-J, et al. Optimal treatment of adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients. Br J Cancer 1994;69:947-951
11. Michalkiewicz E, Sandrini R, Figuereido ECM, et al . Clinical and Outcome Characteristics of Children with Adrenocortical Tumours: A Report from the International Pediatric Adrenocortical Tumor Registry: J Clin Oncol 2004; 22: 838-45.
12. Slooten Hv, Moolenaar AJ, Seters APv, Smeenk D. The treatment of adrenocortical carcinoma with o,p'-DDD: the prognostic implications of serum monitoring. Eur J Clin Oncol 1984;20:47-53.
13. Bugg MF, Ribeiro RC, Roberson PK, Lloyd RV, Sandrini R, Silva JB, et al. Correlation of pathologic features `with clinical outcome in pediatric adrenocortical neoplasia. Am J Clin Pathol 1994;101:625-629.
14. Wood AA, Woodward G. Severe adrenal cortical atrophy (cytotoxic) and hepatic damage produced in dogs by feeding 2,2-bis(parachlorophenyl)=1,1 dichloroethane (DDD or TDE). Arch Pathol 1949;48:387-394.
15. Greig F, Oberfield SE, Levine LS, Ghavimi F, Pang S, New MI. Recovery of adrenal function after treatment of adrenocortical carcinoma with o,p'-DDD. Clin Endocrinol 1984;20:389-399.
16. Korth-Schutz S, Levine LS, Roth JA, Saenger P, New MI. Virilizing adrenal tumour in a child suppressed with dexamethasone for 3 years. Effect of o,p'-DDD on serum and urinary androgens. J Clin Endocrinol Metab 1977;44:433-439.
17. Helson L, Wollner N, Murphy L, Schwartz MK. Metastatic adrenal cortical carcinoma : biochemical changes accompanying clinical regression. Clin Chem 1971;17:1191-1193.
18. Hogan TF, Gilchrist KW, Westring DW, Citrin DL. A Clinical and pathological study of adrenocortical carcinoma. Cancer 1980;45:2880-2883.
19. Bonnacci R, Gigliotti A, Wion-Barbot H, Emy P, Bomnnay M, Callieux AF, et al. Cytotoxic therapy with etoposide and cisplatin in advanced adrenocortical carcinoma. Br J Cancer 1998;78:546-549.
20. Lubitz JA, Freeman L, Okun R. Mitotane use in inoperable adrenal cortical carcinoma. JAMA 1973;223:1109-1112.
21. Seters APv, Moolenaar AJ. Mitotane increases the blood level of hormone-binding proteins. Acta Endocrinol 1991;124:526-533.

22. Slooten Hv, Oosterom ATv. CAP (cyclophosphamide, Doxorubicin and cisplatin) regimen in adrenal cortical carcinoma. Cancer Treat Rep 1983;67:377-379.
23. Ayass M, Gross S, Harper J. High-dose carboplatinum and VP-16 in the treatment of metastatic adrenal carcinoma. Am J Ped Hem Onc 1991;13:470-472.
24. Crock PA, Clark ACL. Combination chemotherapy for Adrenal carcinoma: response in a 5½ year old male. Med Pediatr Oncol 1989;17:62-65.
25. Johnson DH, Greco FA. Treatment of metastatic adrenal cortical carcinoma with cisplatin and etoposide. Cancer 1986;58:2198-2202.
26. Schlumberger M, Brugieres L, Gicquel C, Travagli JP, Droz J-P, Parmentier C. 5-Fluouracil, Doxorubicin and cisplatin for the treatment of adrenal cortical carcinoma. Cancer 1991;67:2997-3000.
27. Haq MM, Legha SS, Samaan NA, Bodey GP, Burgess MA. Cytotoxic chemotherapy in adrenal cortical carcinoma. Cancer Treat Rep 1980;64:909-913.
28. Squire RA, Bianchi A, Jakate SM. Radiation induced sarcoma of the breast in a female adolescent. Cancer 1988;60:2444-2447.
29. Li FP, Fraumeni JF, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, et al. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988;48:5358-5362.
30. Malkin D, Li FP, Strong LC, Fraumeni Jr JF, Nelson CE, Kim DH, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250:1233-1238.
31. Birch JM, Hartley AL, Blair V. Cancer in the families of children with soft tissue sarcoma. Cancer 1990;66:2239-2248.
32. Wagner J, Portwine C, Rabin K, Leclerc J-M, Narod SA, Malkin D. High frequency of germline mutations in childhood adrenocortical cancer. JNCI 1994;86:1707-1710.
33. Latronico AC, Pinto EM, Domenice S, Fragoso MCBV, Martin RM, Zerbini MC, Lucon AM, and Mendonca BB. An inherited mutation outside the highly conserved DNA- binding domain of the p53 tumour suppressor protein in children and adults with sporadic adrenocortical tumors. J Clin Endocrin Metab 2001;86:4970-4973
34. Wiedemann HR. Tumours and hemihypertrophy associated with Wiedemann-Beckwith syndrome. Eur J Pediatr 1983;141:129.
35. Langer P, Cupisti K, Bartsch DK, Nies C, Goretzki PE, Rothmund M, Roher HD. Adrenal involvement in multiple endocrine neoplasia type 1. World J Surg 2002 26: 891-6.
36. Brandi ML, Gagel RF, Angeli A et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001, 86: 5658-71.
37. Doppman JL, Travis WD, Nieman L, Miller DL, Chrousos GP, Gomez MT, Cutler GB Jr, Loriaux DL, Norton JA. Cushing syndrome due to primary pigmented nodular adrenocortical disease: findings at CT and MR imaging. Radiology 1989, 172: 415-20.
38. Dumic M, Ille J, Batinica S, Cacic M, Cvitanovic M, Marinovic B, Plavsic V, Lukenda M, Radica A. Primary adrenocortical micronodular dysplasia. Lijec Vjesn 1999, 121: 22-6.
39. Kirschner LS, Sandrini F, Monbo J, Carney JA, Stratakis CA. Genetic heterogeneity and spectrum of mutations of the PRKAR1A gene in patients with the Carney Complex. Hum Molec Genet 2000, 9: 3037-46.
40. Kushner BH, La Quaglia MP, Bonilla MA, Lindsley K, Rosenfield N, Yeh S, Eddy J, Gerald WL, Heller G, Cheung NK. Highly effective induction therapy for Stage 4 neuroblastoma in children over 1 year of age. J Clin Oncol 1994; 12: 2607-13.

Appendix 1

Suggested Chemotherapy Regimen for Adrenocortical Tumours of Childhood

For children with stage II-IV disease and more than one year of age at diagnosis (modified from ref 40)

Etoposide 600mg/m^2 and Cisplatin 200mg/m^2 per cycle for 3 or 6 cycles according to response.

Chemotherapy to proceed if:

Neutrophil count >1.0 x 10^9/L

Platelet count > 100 x 10^9/L

Glomerular filtration rate > 80ml/min.1.73m^2

If glomerular filtration rate <80ml/min/1.73m^2, consult study co-ordinators.

Day 1	0 hours	Etoposide 200mg/m^2 IV in 500ml/m^2 of 0.9% saline over 2 hours
	2 hours	Commence 1 hour of pre-cisplatin hydration with 0.9% sodium chloride @ 10ml/kg/hr
	3 hours	20 % mannitol 40ml/m^2 over 15 mins
	3 hours 15 mins	Commence cisplatin infusion Cisplatin 50 mg/m^2 In 10ml/kg of 0.9% sodium chloride over 1 hour
	3 hours 15 mins	0.45% saline/2.5% dextrose (3000ml/m^2) plus 60 mmol/m^2 of potassium chloride, 10mmol/m^2 of magnesium sulphate, 2.5mmol/m^2 of calcium gluconate. OVER 24 HOURS At the same time 20 % mannitol 35ml/m^2/hr x 6 hours
Day 2	0 hours	Etoposide 200mg/m^2 IV in 500ml/m^2 of 0.9% saline over 2 hours
	2 hours	Commence 1 hour of pre-cisplatin hydration with 0.9% sodium chloride @ 10ml/kg/hr
	3 hours	20 % mannitol 40ml/m^2 over 15 mins
	3 hours 15 mins	Commence cisplatin infusion Cisplatin 50 mg/m^2 In 10ml/kg of 0.9% sodium chloride over 1 hour
	3 hours 15 mins	0.45% saline/2.5% dextrose (3000ml/m^2) plus 60 mmol/m^2 of potassium chloride, 10mmol/m^2 of magnesium sulphate, 2.5mmol/m^2 of calcium gluconate. OVER 24 HOURS At the same time 20 % mannitol 35ml/m^2/hr x 6 hours

Appendix 1

Day 3	0 hours	Etoposide 200mg/m^2 IV in 500ml/m^2 of 0.9% saline over 2 hours
	2 hours	Commence 1 hour of pre-cisplatin hydration with 0.9% sodium chloride @ 10ml/kg/hr
	3 hours	20 % mannitol 40ml/m^2 over 15 mins
	3 hours 15 mins	Commence cisplatin infusion Cisplatin 50 mg/m^2 In 10ml/kg of 0.9% sodium chloride over 1 hour
	3 hours 15 mins	0.45% saline/2.5% dextrose (3000ml/m^2) plus 60 mmol/m^2 of potassium chloride, 10mmol/m^2 of magnesium sulphate, 2.5mmol/m^2 of calcium gluconate. OVER 24 HOURS At the same time 20 % mannitol 35ml/m^2/hr x 6 hours
Day 4	3 hours 15 mins	Commence cisplatin infusion Cisplatin 50 mg/m^2 In 10ml/kg of 0.9% sodium chloride over 1 hour
	3 hours 15 mins	0.45% saline/2.5% dextrose (3000ml/m^2) plus 60 mmol/m^2 of potassium chloride, 10mmol/m^2 of magnesium sulphate, 2.5mmol/m^2 of calcium gluconate. OVER 24 HOURS At the same time 20 % mannitol 35ml/m^2/hr x 6 hours

During prehydration, cisplatin infusion and post-cisplatin hydration, a careful record of fluid input and output should be kept to prevent fluid overload and ensure diuresis. If diuresis falls below 400ml/m^2/6 hours, frusemide 0.5-1.0mg/kg should be given.

Daily electrolytes including calcium and magnesium G-CSF 5μg/kg/day may be given from day 5 onwards.

CHAPTER TWO

Appendix 2

Recommendations for Mitotane prescription

Mitotane should be started at 1-2 grams/m^2 per day in four daily divided doses and increased by 0.5g-1.0g every 3-5 days as tolerated to a maximum of 8 grams/m^2 per day, until fat stores are saturated and therapeutic levels are achieved.

To saturate the adipose tissue depots as quickly as possible, it is recommended that for the first 30 days, powdered mitotane tablets be mixed with a liquid nutrition formula composed of vegetal fat, such as Pulmocare, an enteral formula recommended for children with cystic fibrosis, or a chocolate milk shake.

Mitotane exhibits a clear dose response curve. Serum levels must be maintained above 14mg/L for effectiveness and below 20mg/L to minimise side-effects. Such measurements, previously available in only some specialist centres cited below but now provided by the drug manufacturer, are vital to keep levels in a narrow therapeutic window [10,21].

- Laboratoire HR Pharma, 19 Rue Frederick Lemaitre, 75020 Paris, France Tel +33 140 331 130 or Fax +33 140331231; e-mail hra-uk@hra-pharma.com
- Dr Peter Heilman, Endocrine Dept, University of Heidelberg, Luisenstrasse 5 - Gebaude 8, 6915 Heidelberg Germany tel : + 06221 568614

Unpleasant side-effects, [e.g. gastrointestinal, neurological, dermal, haematological] are common and very careful monitoring is essential once the fats are saturated *(see below)*

Mitotane readily impairs mineralocorticoid, thyroid, and parathyroid function, and continues or reasserts (previously recovered) suppression of the contralateral adrenal gland. Patients should be monitored regularly with electrolytes and glucose, calcium and thyroid function for the possibility of adrenal crises, particularly during periods of infection.

Patients usually require both glucocorticoid and mineralocorticoid (fludrocortisone) replacement and should be closely followed by an endocrinologist

Functional recovery of the adrenal zona glomerulosa and fasciculata has been reported following Mitotane therapy.

Adverse Reactions to Mitotane

i. Gastrointestinal:
Anorexia, vomiting, diarrhoea

ii. Neurological disturbances:
Lethargy, dizziness, somnolence, muscle weakness, headache, confusion, speech impairment, ataxia, neuropathy, mood changes and rarely coma.

iii. Dermal:
Rash, alopecia, pigmentation

iv. Miscellaneous:
Leukopenia, thrombocytopenia, hyperbilirubinaemia, retinopathy

CHAPTER THREE

Chapter 3 - Differentiated Thyroid Cancer (DTC)

3.1 Executive Summary

Main Issues

Differentiated thyroid cancer (DTC) in childhood and adolescence has an excellent prognosis even if there is extensive disease at presentation.

Children usually present with a solitary or dominant thyroid nodule but malignancy can be present in what appears clinically to be a diffuse or simple multinodular goitre.

Children at risk include those exposed to ionising irradiation of the thyroid and/or with a genetic predispoition (eg Familial Adenomatous Polyposis (FAP), Cowden's disease, the Carney complex, dominant papillary carcinoma families)

Ultrasound and isotope scans of thyroid swellings rarely alter clinical management. CT or MR scanning of the thyroid is not routinely indicated and if performed, iodine conaining contrast media should be avoided.

In young children, the positive predictive value of fine needle aspiration (FNA) is low, and the procedure requires a general anaesthetic, whereas in older adolescents, the procedure may be well tolerated and a positive cytological diagnosis can guide further management.

The extent of surgery for differentiated thyroid cancer (particularly microcarcinomas) with no evidence of lymph node or distant metastases, is controversial.

Main Recommendations

All euthyroid children with thyroid enlargement should be referred to a tertiary paediatric endocrinologist linked to a UKCCSG centre for assessment and exclusion of a potential malignant lesion which may even exist within a diffuse or multinodular goitre.

A thyroid nodule should be considered an indication for surgical intervention. FNA should not delay a definitive surgical procedure.

The treatment plan should be discussed at the adult cancer centre thyroid MDT, prior to any surgical intervention.

In the presence of both a thyroid swelling and clinically abnormal cervical lymphadenopathy, FNA biopsy of both the lymph node and the thyroid should be undertaken.

Parents/carers, and the children themselves where appropriate, must be fully informed of the implications and risks of thyroid surgery.

Surgery should be performed by a specialist thyroid surgeon with interest and expertise in the management of thyroid cancer, and nominated by the centre.

The objective of surgery in DTC is to remove all macroscopic malignant disease in the thyroid, draining lymph nodes and involved adjacent structures, and minimise complications.

The minimum operation for the diagnosis and/or treatment of an isolated or dominant thyroid nodule is total lobectomy and isthmectomy. Lymph node dissection is not indicated in unproven malignancy.

CHAPTER THREE

Differentiated thyroid cancer is a reputedly more aggressive disease in younger patients, and so total or near-total thyroidectomy with subsequent therapeutic radioidine is advised in patients under 10 years of age.

Adolescents with microcarcinomas (<1cm) and no evidence of disease elsewhere can probably be safely treated like adults, with total lobectomy alone.

Facilities and a written protocol must be available for the management of airway obstruction associated with postoperative haemorrhage, and the monitoring and treatment of hypocalcaemia, which should begin 4hours post-operatively.

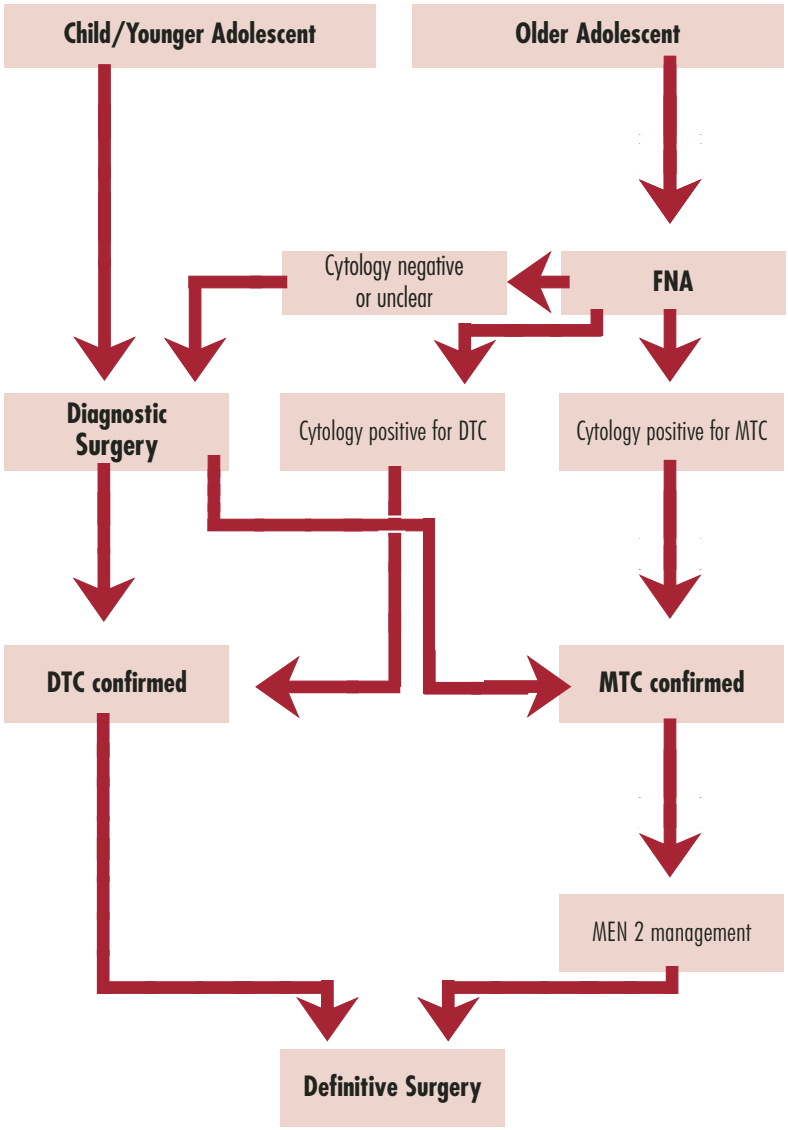
It is good practice to assess the voice/vocal cord mobility after surgery by referral to an ENT surgen.

Life-long suppressive thyroxine therapy is the key adjuvant therapy following total or near-total thyroidectomy for papillary or follicular cancer. This should be started under the guidance of the paediatric endocrinologist and dose-titrated to maintain serum TSH below 0.1mU/l.

After ablative therapy, regular measurement of serum thyroglobulin is a valuable screen for residual or recurrent disease, which can be treated with therapeutic radioiodine.

Follow-up must be **life-long**, to monitor thyroid replacement therapy, to screen for recurrence, and to monitor late effects of therapy.

Diagnostic Flow Chart for the Child with Nodular Thyroid Disease



DTC Differentiated Thyroid Carcinoma
MTC Medullary Thyroid Carcinoma

CHAPTER THREE

3.2 Introduction and UK Registry Data

Thyroid cancer in children is rare, with an annual incidence of 0.5/million/year, equivalent to 5 new cases annually in England and Wales[1,2]

Only 5-10% of all thyroid cancers occur in childhood, predominantly in female adolescents.

More than 90% of childhood thyroid cancers are differentiated.

Differentiated thyroid cancer (DTC) in children includes:
papillary carcinoma (80-90%),
follicular cancers (5-15%) - much less common than in adults,
rare aggressive histological sub-types of differentiated thyroid cancer .

Children usually present with a solitary or dominant thyroid nodule but malignancy can be present in what appears clinically to be a diffuse or simple multinodular goitre.

Although children with differentiated thyroid carcinomas may present with extensive disease, it is rarely fatal[3-7]. There is 100 % survival for all registered UK cases.(National Registry of Childhood Tumours)

Thyroid Cancer Registrations in National Registry of Childhood Tumours 1971-2000

Table 1 Number of Thyroid Cancer Registrations by Tumour Histology, 1971-2002

	Total	Male	Female	0-4years	5-9years	10-14years
Total	171	53	118	7	33	31
Differentiated	28	38	90	2	27	99
Anaplastic	1	0	1	0	0	1
Medullary	42	15	27	5	6	31

Overall age standardised incidence rate was 0.4 per million. Differentiated (papillary and follicular) thyroid carcinoma accounted for 75%; there was a single case of anaplastic carcinoma. There was a female excess for both main histological categories. Girls accounted for 71% of differentiated cases but the female excess was less marked below age 10 years (60%) than at age 10-14 (74%).

Table 2 Thyroid Cancer Survival byTumour Differentiation, 1971-2002

Differentiated	10 year actuarial survival 100%
Anaplastic	1 case dead 3 years 7 months

Predisposing factors to DTC include history of neck irradiation[8-11], and genetic disorders (eg Familial Adenomatous Polyposis[12], Cowden's disease[13] .)

5-10% of childhood thyroid cancer are Medullary Thyroid Carcinomas (MTC), which should be considered diagnostic of Multiple Endocrine Neoplasia type 2 (MEN 2)

3.3 Clinical Presentation

Children who are subsequently proven to have thyroid cancer present with:

- thyroid swelling
- cervical lymphadenopathy (or, very rarely, pulmonary metastases)
- assessment of the thyroid following irradiation (environmental or therapeutic,eg via a late effects clinic)
- surveillance in known kindred of familial thyroid cancer.

3.4 Statement of Best Practice

All euthyroid children with thyroid enlargement should be referred to a tertiary paediatric endocrinologist linked to a UKCCSG centre for assessment and exclusion of a potential malignant lesion which may even exist within a diffuse or multinodular goitre. The initial investigation and treatment should be undertaken by a designated paediatric endocrinologist and experienced thyroid surgeon nominated by the centre. Where the diagnosis of malignancy has been confirmed, subsequent management should be undertaken with involvement of additional multidisciplinary team members including a paediatric oncologist, a clinical oncologist (or nuclear medicine physician) with a special interest in thyroid cancer, and a clinical geneticist.

3.5 Diagnostic Investigations

i. Family History

A full history may reveal a familial disorder and is necessary in all children. This should include 1st , 2nd, and preferably also 3rd degree relatives of affected individuals.

ii. Clinical Examination

Clinical examination of the neck is required to identify palpable abnormalities in the thyroid, adjacent structures and related lymph nodes.

iii. Investigations

a. Biochemistry

- Thyroid function tests (TSH, FT_4 +/- FT_3) and thyroid autoantibody status
- Serum calcium

b. Radiology

- Chest XR will not alter initial management .
- Ultrasound scans may be useful to distinguish thyroid nodules from congenital cystic anomalies in the neck. Routine CT or MR scanning of thyroid nodules is not indicated.

3.6 Pre-Operative Management

i. Cytology - Fine needle aspiration (FNA)

In young children, the positive predictive value of FNA is low and thus of doubtful clinical value. A thyroid nodule should be considered an indication for surgical intervention[14,15].

FNA should be considered in older adolescent patients who can usually tolerate the procedure, since a positive cytological diagnosis can guide further management[16-20]. False negative results can occur, particularly in patients with a history of radiation exposure.

FNA should be carried out by a clinician with expertise in this procedure and the cytology should be reported by a cytopathologist who has a special interest in thyroid disease[21].

In the presence of both a thyroid swelling and clinically abnormal cervical lymphadenopathy, FNA biopsy of both the lymph node and the thyroid should be undertaken.

FNA should not delay a definitive surgical procedure. Where there are strong clinical grounds for suspicion of malignancy, surgical intervention is mandatory.

FNA may occasionally suggest a diagnosis of medullary thyroid cancer (MTC) *(see MEN2 chapter 5.)*

If thyroid cancer has been histopathologically confirmed from cervical lymph node biopsy, no further diagnostic procedures are required, prior to definitive surgical treatment.

ii. Preparation for Thyroid Surgery

Direct or indirect laryngoscopy to assess preoperative vocal cord function is good practice in the older child.

Parents/carers, and the children themselves where appropriate, must be fully informed of the implications and risks of thyroid surgery. These include:

- the surgical scar,
- the possibility of lifelong thyroxine supplements,
- post-operative haemorrhage necessitating emergency re-operation,
- voice change, respiratory distress, or difficulty swallowing, which might result from temporary or permanent damage to the recurrent laryngeal nerves or external branch of the superior laryngeal nerves,
- hypocalcaemia which may be temporary or permanent requiring treatment with calcium and/or vitamin D supplements
- a further therapeutic surgical procedure consequent upon the diagnosis of malignancy,
- lymph node dissection is associated with an increased risk of hypocalcaemia and recurrent laryngeal nerve injury.

3.7 Operative Management

The treatment plan should be discussed at the adult cancer centre thyroid MDT meeting, prior to intervention[22,23]. Members of the specialist paediatric team not in regular attendance at the thyroid MDT should attend for discussion of individual paediatric cases.

Surgery should minimise the risk of avoidable injury to the recurrent and superior laryngeal nerves, and attempt to conserve functioning parathyroid tissue. It should be carried out by a specialist thyroid surgeon.

i. Diagnostic Surgery

The minimum intervention for a patient with a thyroid nodule is thyroid lobectomy and isthmectomy. This avoids the increased risk of recurrent laryngeal nerve and parathyroid damage associated with re-operation and is curative in some cases of DTC[24].

In the absence of a prior diagnosis, the value of frozen section examination is unclear but may confirm a previous clinical suspicion of papillary thyroid carcinoma. This possibility should be discussed with the thyroid pathologist pre-operatively.

Lymph node dissection is not indicated in unproven malignancy[25,26]. In patients with cervical lymphadenopathy and a thyroid mass, frozen section examination of abnormal lymph nodes is advised, to confirm the presence of metastatic disease, before continuing to definitive lymph node surgery.

ii.

Definitive Surgery [27-29]

The minimum operation for the diagnosis or treatment of an isolated/dominant thyroid nodule is total lobectomy and isthmectomy.

In many cases total or near-total thyroidectomy will eventually be required, once the diagnosis is confirmed.

Total thyroidectomy is indicated for confirmed carcinoma, where there is a history of prior neck irradiation.

Children with lymph node metastases should be managed by central compartment node dissection and biopsy of a suitable lateral compartment node. If this node is involved then lateral compartment neck dissection should be performed (selective neck dissection). Radical forms of block dissection of the neck which sacrifice non lymphatic structures are not indicated unless those structures are infiltrated with tumour[34].

a.

Papillary Carcinoma

The objective of surgery in DTC is to remove all macroscopic malignant disease in the thyroid, involved draining lymph nodes and involved adjacent structures.

If frozen section histology demonstrates papillary carcinoma, total thyroidectomy can be performed thereby eliminating the need for a second surgical procedure.

Because thyroid cancer in children under 10 years of age is reputedly more aggressive than in adults, (overt lymphadenopathy and lung metastases are more common at presentation) a total or near-total thyroidectomy with subsequent radioidine is advised in all children and adolescents with tumours >1cm in diameter [9,30-32]. This is controversial in microcarcinomas (<1cm in diameter). Adolescents with microcarcinoma but without lymphadenopathy, clinically overt disease in the contralateral lobe or evidence of distant metastases, can probably be safely treated like adults, by total lobectomy alone[33].

In DTC in children, there is no consensus on the role of lymph node dissection in the absence of clinically evident lymph node disease, but the surgeon should have a low threshold for central compartment node dissection.

Children with lymph node metastases should be managed by central compartment node dissection and biopsy of a suitable lateral compartment node. If this node is involved then lateral compartment neck dissection should be performed (selective neck dissection) Radical forms of block dissection of the neck which sacrifice non lymphatic structures are not indicated unless those structures are infiltrated with tumour[34].

The following terms for lymph node surgery should be used:

Central compartment		
Level	6	Pre and paratracheal nodes
Lateral compartment -		
Levels	1	Submental and submandibular nodes
Level	2	Cervical chain nodes above the level of the thyroid. Further divided by their relationship to the accessory nerve - 2a (below) and 2b (above)
Level	3	Cervical chain nodes from the level of the thyroid to the level of the cricoid.
Level	4	Cervical chain nodes from the level of the cricoid to the suprasternal notch.
Level	5	Posterior triangle nodes. Can be divided by their relationship to the omohyoid muscle into 5a (above) and 5b (below)
Level	6	Central compartment nodes
Level	7	Superior mediastinal nodes

Selective neck dissection
This preserves the submandibular gland, sternomastoid muscle, the accessory nerve and the internal jugular vein. One or more levels of the neck (1-5) are dissected and the neck dissection labelled accordingly, i.e. levels 2-5 or 3-5.

b.

Follicular carcinoma

It is not possible by FNAC alone to determine whether a follicular lesion is benign or malignant. Thus all such lesions require a diagnostic thyroid lobectomy and isthmectomy and formal histology. Where histology confirms a benign follicular adenoma and there is no histological evidence of capsular or vascular invasion, lobectomy is sufficient treatment[35].

When diagnostic lobectomy and histology reveals a follicular carcinoma with capsular invasion alone, the MDT should decide whether further surgery and completion thryoidectomy is required. If definitive histology reveals both capsular and vascular invasion or frankly invasive disease completion thyroidectomy (and radioiodine ablation) is advised.

3.8 Postoperative Medical Management

Facilities and a written protocol must be available for the management of airway obstruction or wound haemorrhage after surgery.

Temporary postoperative hypocalcaemia occurs after total/near total thyroidectomy more frequently in children than in adults[3,36]. Serum calcium should be measured 4-hours post-operatively and then 12 hourly for 24-48 hours. Oral calcium supplementation should be commenced if the corrected serum calcium levels fall below 2mmoL/l. At corrected serum calcium below 1.9mmoL/L, slow intravenous calcium infusions should be administered.

Where hypocalcaemia persists beyond the first 48 post-operative hours, PTH levels should be measured and Vitamin D supplementation commenced (alfacalcidol or calcitriol). The child should not be discharged until the calcium level is stable without need of intravenous calcium administration in the preceding 24 hours.

All children who have had total or near total thyroidectomy for DTC will require suppressive thyroxine therapy titrated approximately 6-weekly to maintain TSH below 0.1mU/l.

Replacement thyroxine therapy should be commenced 3 days after total thyroidectomy under the guidance of the paediatric endocrinologist. If the interval to planned ^{131}I ablation is longer than two weeks, tri-iodothyronine (T_3) which has a shorter half-life than thyroxine (T_4), is preferred initially. *(see radiodine section)*

It is good practice to assess the voice/vocal cord mobility after surgery by referral to a paediatric ENT surgeon.

^{131}I ablation should only be employed after total/near total thyroidectomy.

3.9 Pathology/Staging

The pathological stage of all differentiated thyroid tumours should be recorded and registered with the UKCCSG.

The paediatric pathologist may wish to consult with the MDT designated adult thyroid pathologist.

pTNM staging (AJCC, fifth edition, 1997) for DTC

	Primary Tumour
pT0	No evidence of primary tumour
pT1	Intrathyroidal tumour < 1 cm in greatest dimension
pT2	Intrathyroidal tumour > 1cm to 4 cm in greatest dimension limited to thyroid
pT3	Intrathyroidal tumour > 4 cm in greatest dimension limited to thyroid
pT4	Tumour of any size extending beyond the thyroid capsule
pTX	Primary tumour cannot be assessed
	Regional Lymph Nodes (cervical and upper mediastinal)
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
	• N1a metastasis in ipsilateral cervical nodes
	• N1b metastasis in bilateral, midline or contralateral cervical or superior mediastinal nodes
	Distant Metastases
MX	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

3.10 Post-Operative Radioiodine ^{131}I Therapy

Although DTC in pre-adolescent children is reputedly more aggressive than in older adolescents, the role of radioiodine (^{131}I) ablation to any thyroid remnant following total thyroidectomy for small (<1cm) intra-thyroidal primary tumours in children is not known[37]. This should be discussed in the thyroid MDT with the clinical oncologist for individual cases.

Post-operative ^{131}I ablation of residual thyroid tissue reduces local recurrence and, because of its safety and tolerability, is recommended for all children and adolescents with DTC larger than 1cm in diameter[27,35,38] following total / near total thyroidectomy. This regimen allows post-treatment surveillance with thyroglobulin (Tg) measurements and identification and treatment of any metastases with further ablative ^{131}I therapy.

Ablative ^{131}I therapy should be performed in a suitably equipped centre which offers open access during therapy, and after full discussion with the family about potential rare, but important, short and longer term side-effects. These are dose-related and the cumulative activity should therefore be kept as low as possible[29,39]. The adult recommended dose is 3.7GBq, increasing to 5.5GBq for refractory disease. Doses for children should be calculated as a percentage of the adult dose, based on body weight in comparison to the average adult weight of 70kg.

In adolescent girls, pregnancy must be excluded before ^{131}I is given and avoided for at least 6 and preferably 12 months[40].

In peri-pubertal adolescent boys, particularly those likely to receive more than two ablative radioiodine therapy doses, consideration should be given to pre-treatment semen cryopreservation[41]. Sperm damage can be reduced by ensuring good hydration during treatment.

Serum TSH and thyroglobulin (Tg) should be measured immediately prior to ^{131}I ablation.

T_3 therapy should be discontinued at least 2 weeks, and T_4 at least 4 weeks prior to the planned ablation therapy. In either case there should be opportunity for the TSH level to rise to above 30 mU/l to ensure adequate ^{131}I uptake.

If iodine-containing contrast media have been used in preoperative imaging, it may be appropriate to delay the ^{131}I therapy for up to 3 months in order to ensure its maximum uptake by any residual disease. ^{123}I may be more sensitive and less prone to induce 'stunning' than ^{131}I. A neck plus whole body scan should be performed at 48-72h after the ablative dose of ^{131}I.

3 days after ablative ^{131}I therapy the child should be started on suppressive T_4 replacement, and should be reviewed 4-6 weeks later to monitor FT_4 (and/ or FT_3) and TSH levels and to arrange scans.

Serial thyroglobulin (Tg) measurements commencing 4-6 months after ablation therapy whilst on suppressive thyroxine doses are used to exclude residual disease. In adult centres there is a move to use stimulated thyroglobulin measurements, by thyroid hormone withdrawal or recombinant TSH (rhTSH), as a follow-up investigation. There are few data regarding the use of rhTSH in children.

If thyroglobulin is elevated, further ^{131}I ablative doses may be required. Diagnostic ^{131}I scanning is reserved for patients with antithyroglobulin antibodies, or with a high index of suspicion of residual/recurrent tumour. Before a diagnostic radioidine scan, patients should switch from T_4 to T_3 replacement and a low iodine diet advised. T_4 is routinely stopped 4 weeks and T_3 2 weeks before a diagnostic scan.

There is no further need for radioisotope scans unless there is evidence of residual or progressive disease, or a rising serum Tg, in which case scans should be reassessed every 6-12month together with serum Tg measurements.

3.11 Short to Medium Term Surveillance

Patients should be seen in a specialist MDT setting, by a member of the MDT working according to local guidelines, approximately every 3-6 months for the first two years, 6-monthly for the next 3 years and annually thereafter.

T_4 should be used in preference to T_3 for long term TSH suppression.

All children should have FT_4 (and/ or FT_3) and TSH levels checked at follow up and supervised by the endocrinologist or other member of the MDT, in order to:

- monitor non-compliance or potential for hyperthyroidism,
- assess the adequacy of TSH elevation to >30mU/l before any ^{131}I ablation therapy
- assess the adequacy of TSH suppression to levels below 0.1mU/l after total thyroidectomy.
- ensure serum FT_3 levels are maintained within the normal range, even at the expense of a mildly elevated FT_4.
- In patients receiving tri-iodothyronine (T_3) therapy, serum FT_3 (not FT_4) and TSH need to be measured.

Serum thyroglobulin (Tg), - together with FT_4, and TSH to aid interpretation - should be measured 3 months after total thyroidectomy and ^{131}I ablation, and subsequently 3-6 monthly in the same laboratory using the same method, during TSH suppression or whenever TSH is raised before a diagnostic scan. Tg elevations in this context are highly suggestive of recurrent disease.

Any child on calcium or vitamin D therapy requires close monitoring of serum calcium in a specialist clinic to prevent hypercalcaemia.

Six-monthly paediatric endocrine follow-up to adulthood is necessary to ensure optimal growth and age-appropriate development .

3.12 Long Term Care and Surveillance

Life-long annual surveillance in a specialist clinic is required for all patients because:

- the disease has a long natural history,
- late recurrences can occur, which can be successfully treated with a view to cure or long-term survival[6,42,43],
- the consequences of supraphysiological T_4 replacement (such as atrial fibrillation and osteoporosis) need long term monitoring,
- late effects of ^{131}I treatment appear unlikely[44], but may yet develop after large or repeated radioiodine doses in very young children. From data based on adults these include subfertility[45], leukaemia[46], and second malignancies[39,40,47-49]. The outcome of subsequent pregnancies is excellent[50].

3.13 Genetic Management

A full family history should include 1st, 2nd and 3rd degree relatives.
DTC can occur as part of -

- Familial adenomatous polyposis (FAP)[12]
- Cowden's disease[13]
- The Carney Complex[51,52]
- Dominant papillary carcinoma families

Clinical examination for features associated with Cowden's disease, the Carney Complex, and Gardner's syndrome (FAP) is neccassary.

Papillary carcinoma with a cribriform histology is highly suggestive of familial adenomatous polyposis (FAP)[53]. Referral to genetics is indicated. Annual sigmoidoscopy should be initiated from 12 years of age[53].

Follicular carcinoma in a patient with multinodular goitre and/or follicular adenomas should raise the possibility of Cowden's disease. Referral to clinical genetic services and PTEN mutation analysis should be considered.

3.14 Treatment of Recurrent Disease

Early detection of recurrent disease by thyroglobulin monitoring and regular clinical surveillance can lead to long term survival and potential cure.

Recurrence may be suggested by the presence of palpable disease, rising thyroglobulin levels or follow up radioiodine scanning.

The management plan should be discussed with the specialist MDT.

Rising thyroglobulin levels should always be interpreted with care due to variation between laboratories and the confounding effects of antibodies.

The absence of a rise in thyroglobulin does not exclude recurrent disease, but false iodine scan positivity should be excluded before administering further ^{131}I therapy.

Treatment options for recurrent disease within the neck is primarily surgical re-exploration with ablative ^{131}I therapy and if this strategy fails, consideration of external beam radiotherapy.

The extent of recurrence should be assessed by cross-sectional imaging prior to intervention. If CT is used, iodine-based contrast media should be avoided as this and diagnostic tracer iodine scans may reduce uptake of subsequent therapeutic radioiodine.

Inoperable metastatic disease should be treated with repeated ablative doses of ^{131}I therapy at 4-6 monthly intervals, ensuring normal pre-treatment haematology and renal function. No maximum limit to cumulative doses ^{131}I therapy for persistent disease has been stated.

A neck and whole body scan 3 days after ^{131}I administration provides assessment of disease uptake.

False negative scans occur in situations where there is inadequate TSH elevation, iodine contamination by drugs or contrast material.

Rarely persistent and worsening Tg elevation in the absence of iodine scan positivity may necessitate further radiological (CT chest) or PET scans and consideration of a therapeutic dose of radioiodine. A 3-day post-treatment scan should be included.

Radical dose external beam radiotherapy is valuable for inoperable microscopic residual, or macroscopic tumour, which is non iodine-avid.

3.15 Information and Support for Patients and Carers

Patients may find the following web-sites and contact organisations useful:

- British Thyroid Foundation, PO Box 97, Clifford, Wetherby, West Yorkshire LS23 6XD **www.btf-thyroid.org**
- Thyroid Cancer Survivor's Association **www.thyca.org**
- British Thyroid Association Links Page **www.british-thyroid-association.org**

3.16 Registration and Tumour Banking

All children with thyroid cancer should be followed up in collaboration with the Children's Cancer Centre, and should be registered with the UKCCSG by their paediatric endocrinologist or oncologist.

Any genetic/familial cancers should be highlighted in linked familial cancer databases.

Consent to Tumour Banking - as per UKCCSG protocol - is encouraged.

CHAPTER THREE

References

1. Stiller CA. International variations in the incidence of childhood carcinomas. Cancer Epidemiol Biomark Prevent 1984; 3:305-310.
2. Harach HR, Williams ED. Childhood thyroid cancer in England & Wales. Br J Cancer 1995; 72:777-783.
3. La Quaglia M, Corbally MT, Heller G et al. Recurrence and morbidity in differentiated thyroid cancer in children. Surgery 1988; 104:1149-1156.
4. Polyakov VG, Durnor LA, Lebedev VI, Lebedinsky AV. Thyroid cancer in children. Med Pediatr Oncol 1991; 19:386(abstr).
5. Massimino M et al. Primary thyroid carcinoma in children: a retrospective study of 20 patients. Med Pediatr Oncol 1995; 24:13-17.
6. Vassilopolou-Sellin R, Goepfert H, Raney B, Schultz PN. Differentiated thyroid cancer in children and adolescents: clinical outcome and mortality after long-term follow-up. Head & Neck1998; 20:549-555.
7. Allessandri AJ, Goddard KJ, Blair GK, Fryer CJH, Schultz KR. Age is the major determinantof recurrence in differentiated thyroid carcinoma. Med Pediatr Oncol 2000; 35:41-46.
8. Duffy BJ Jr, Fitzgerald PJ. Cancer of the thyroid in children. A report of 28 cases. J Clin Endocrinol 1950; 3:1018-1032.
9. Schlumberger MJ, De Vathaire F, Travagli JP et al. Differentiated thyroid carcinoma in childhood: long term follow-up of 72 patients. J Clin Endocrinol Metab 1987; 65:1088-1094.
10. Ron E, Lubin JH, Shore RE et al. Thyroid cancer after exposure to external irradiation. A pooled analysis of seven studies. Radiat Res 1995; 141:259-277.
11. Sklar C, Whitton J, Mertens A et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the childhood cancer survivor study. J Clin Endocrinol Metab 2000; 85:3227-3232.
12. Bell B, Mazzaferri EL. Familial adenomatous polyposis (Gardner's syndrome) and thyroid carcinoma: a case report and review of the literature. Dig Dis Sci 1996; 38:185-190.
13. Michaels RD, Shakir KMM. Association of multinodular goitre with breast carcinoma: Cowden's disease. J Endocrinol Invest 1993; 16:909-911.
14. Hung W, Anderson KD, Chandra RS et al. Solitary thyroid nodules in 71 children and adolescents. J Pediatr Surg 1992; 27:1407-1409.
15. Degnan BM, McClellan DR, Francis GL. An analysis of fine needle aspiration biopsy of the thyroid in children and adolescents. J Pediatr Surg 1996; 31:903-907.
16. Fowler CL, Pokorny WJ, Harbert FJ. Thyroid nodules in children: current profile of a changing disease. South Med J 1989; 82:1472-1478. Silverman JF, Gurley M, Holbrook CT. Pediatric fine needle aspiration biopsy. Am J Clin Pathol 1990; 95:653-659.
17. Pironalli D, Martelli G, Del Prato I et al. The role of fine needle aspiration in the diagnosis of thyroid nodules: analysis of 795 consecutive cases. J Surg Oncol 1992; 50:247-250.
18. Raab SS, Silverman JF, Elsheikh TM et al. Pediatric thyroid nodules: disease demographics and clinical management as determined by fine needle aspiration biopsy. Pediatrics 1995; 95:46-49.
19. Cap J, Ryska A, Rehorkova P et al. Sensitivity and specificity of the fine needle aspiration biopsy of the thyroid: clinical point of view. Clin Endocrinol 1999; 51:509-515.
20. Guidelines for the management of thyroid cancer in adults. British Thyroid Association, Royal College of Physicians, 2002
21. Hardy KJ, Walker BR, Lindsay RS et al. Thyroid cancer management. Clin Endocrinol 1995;42:651-655.
22. Vanderpump MPJ, Alexander L, Scarpello JHB, Clayton RN. An audit of the management of thyroid cancer in a district general hospital. Clin Endocrinol 1998; 48:419-424.
23. Bi J, Lu B. Advances in diagnosis and management of thyroid neoplasms. Curr Opin Oncol 2000; 12:54-59.

24. Hundahl SA, Cady B, Cunningham MP et al. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the United States during 1996. US and German Thyroid Cancer Study Group. An American College of Surgeons Cancer Patient Care Evaluation Study. Cancer 2000; 89:202-217.
25. Van de Velde CJH, Hamming JF, Goslings BM et al. Report of the consensus development conference on the management of differentiated thyroid cancer in the Netherlands.Eur J Cancer Clin Oncol 1988; 24:287-292.
26. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994; 97:418-428
27. Mazzaferri EL. An overview of the management of papillary and follicular thyroid carcinoma. Thyroid 1999; 9(5):421-427.
28. Schlumberger MJ. Papillary and follicular thyroid cancer. N Engl J Med 1998; 338:297-306.
29. Zimmerman D, HayID, Gough IR et al. Papillary thyroid carcinoma in children and adults: long-term follow-up of 1039 patients conservatively treated at one institution during three decades. Surgery 1988; 104:1157-1166.
30. La Quaglia MP, Black T, Holcomb GW et al. 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. J Pediatr Surg 2000; 35:955-959
31. Jarzab B, Handkiewicz Junak D, Wloch J et al. Multivariate analysis of prognostic factors for differentiated thyroid carcinoma in children. Eur J Nucl Med 2000; 27:833-841.
32. Guidelines for the surgical management of endocrine disease and training requirements for endocrine surgery. British Association of Endocrine Surgeons. 2000.
33. La Quaglia MP, Telander RL. Differentiated and medullary thyroid cancer in childhood and adolescence. Sem Pediatr Surg 1997; 6:42-49.
34. Tsang RW, Brierly JD, Simpson WJ et al . The effects of surgery, radioiodine and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma.Cancer 1998; 82:375-388.
35. Stael AP, Plukker JT, Piers DA et al. Total thyroidectomy in the treatment of thyroid carcinoma in childhood. Br J Surg 1995; 82:1083-1085.
36. Hung W, Sarlas N. Current controversies in the management of paediatric patients with well differentiated non-medullary thyroid cancer: a review. Thyroid 2002; 12:683-702.
37. De Groot LJ, Kaplan EL, McCormick M, Strauss FH. Natural history, treatment and course of papillary thyroid cancer. J Clin Endocrinol Metab 1990; 71:414-424.
38. Rubino C, de Vathaire F, Dottorini ME et al. Second primary malignancies in thyroid cancer patients. Br J Cancer 2003; 89:1638-1644.
39. Dottorini ME, Lomuscio G, Mazzucchelli L et al. Assessment of female fertility and carcinogenesis after iodine I131 therapy for differentiated thyroid cancer. J Nucl Med 1995; 36:21-27.
40. Vini L, Harmer C. Radioidine treatment for differentiated thyroid cancer.J Clin Oncol 2000; 12:365-372.
41. Balazs G, Gyory F, Lukacs G, Szakall S. Long-term follow-up of node-positive papillary thyroid carcinomas. Langenbecks Arch Surg 1998; 383:180-182.
42. Newman K, Black T, Heller G et al. Differentiated thyroid cancer: determinants of disease progression in patients less than 21 years of age at diagnosis: a report from the Surgical Discipline Committee of the Children's Cancer Group. Ann Surg 1998; 227:533-541.
43. Hall P, Mattson A, Boice JD Jr. Thyroid cancer after diagnostic administration of iodine-131. Radiat Res 1996; 145:86-92.
44. Vini L, Pratt B, Al-Saadi A et al. Fertility after Iodine-131 therapy for thyroid cancer. Br J Cancer 1998; 78(suppl. 2):16.
45. Hall B, Boice JD Jr, Berg G et al. Leukaemia incidents after Iodine-131 exposure.Lancet 1992; 340:1-4.

46. Edmonds CJ, Smith T. The long-term hazards of the treatment of thyroid cancer with radioiodine. Br J Radiol 1986; 59:45-51.
47. Maxon HR, Smith HS. Radioiodine-131 in the diagnosis and treatment of metastatic well differentiated thyroid cancer. Endocrinol Metab Clin North Am 1990; 19:685-718.
48. De Vathaire F, Schlumberger MJ, Delisle MJ et al. Leukaemia and cancers following iodine ^{131}I administration for thyroid cancer. Br J Cancer 1997; 75:734-739.
49. Schlumberger MJ, De Vathaire F, Cecarelli C et al. Exposure to radioiodine (^{131}I) for scintigraphy or therapy does not preclude pregnancy in thyroid cancer patients. J Nucl Med 1996; 37:606-612.
50. Carney JA. Gastric stromal sarcoma, pulmonary chondroma, and extra adrenal paraganglioma (Carney triad): natural history, adrenocortical component, and possible familial occurrence. Mayo Clin Proc 1999; 74: 543-52.
51. Carney JA, Stratakis CA. Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet 2002; 108:132-139.
52. Fenton PA, Clarke SEM, Owen W et al. Cribriform variant of papillary thyroid cancer: a characteristic of familial adenomatous polyposis. Thyroid 2001; 11:193-197.

CHAPTER FOUR

Chapter 4 - Phaeochromocytoma

4.1 Executive Summary

Main Issues

Phaeochromocytomas are rare in children and adolescents, accounting for 10-20% of the national prevalence of this disease.

They are often multiple or bilateral, but malignancy is rare in childhood (<6%), especially when part of Multiple Endocrine Neoplasia Type 2 (MEN 2) syndromes.

15% cases present with an incidental adrenal mass or as a result of screening at risk family members.

Almost all paediatric phaeochromocytomas occur as a result of a genetic predisposition.

There should be a high index of suspicion for phaechromocytoma in any child persenting with paroxysmal symptoms as such cases may be difficult to diagnose.

The prognosis is excellent but malignancy cannot be excluded on histology and metachronous tumours occur.

Main Recommendations

Suspected or confirmed phaeochromocytomas must be referred without delay to a regional specialist paediatric endocrine and UKCCSG centre with appropriate medical and surgical expertise.

The diagnosis of phaeochromocytoma requires specific biochemical and radiological investigations. Negative results do not exclude the diagnosis and repeated investigation may be necessary.

It is important to take a careful family history, examine the patient and request gene mutation analysis for MEN 2, neurofibromatosis type I (NF-1), Von-Hippel Lindau (VHL) and paraganglioma syndromes (SDH subunits B, C and D).

Most children require urgent transfer to a tertiary centre before commencing α blockade. It may be commenced before transfer in discussion with the tertiary centre. β adrenergic blockade, **if required**, should only be administered **after** full α blockade has been achieved.

Routine selective venous sampling for localisation is not indicated.

Under no circumstances should image-guided or open biopsy be attempted.

Surgical procedures should only be undertaken when full preoperative cardiovascular stabilisation (α blockade) has been achieved.

Surgery must be carried out by an experienced surgeon recommended by the local multidisciplinary team (MDT).

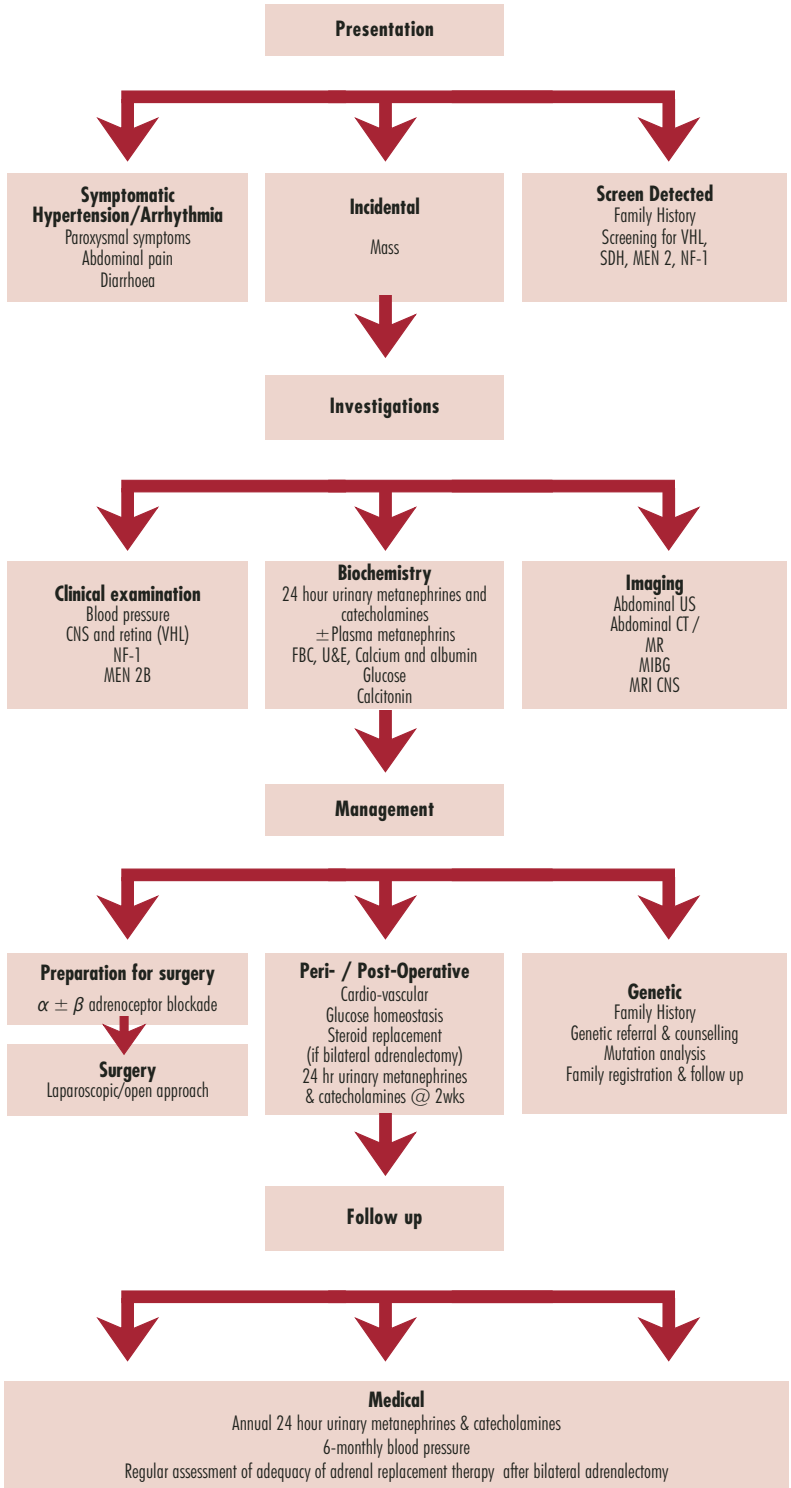
Facilities and written guidelines must be available for the pre and peri-operative management, in particular the management of hypertension with α and β adrenergic blockade.

All patients should be referred for genetic counselling and mutation analysis to their local regional genetics service.

Follow-up and screening should be lifelong to exclude metachronous tumours.

Data collection through central registration is mandatory to increase further understanding of this disease and its associated syndromes.

Diagnostic Flow Chart for Phaeochromocytoma



CHAPTER FOUR

4.2 Introduction and UK Registry Data

Phaeochromocytomas are rare tumours with an annual incidence of 1 to 2 per million.

10-20% of phaeochromocytomas occur in children and adolescents.

Less than 6% of paediatric phaeochromocytomas are malignant.

Paediatric phaeochromocytomas are often multiple / bilateral and occur as a result of a genetically determined predisposition.

Even in the absence of a specific genetic diagnosis there is a likelihood of an underlying genetic susceptibility and lifelong follow up is recommended.

The prognosis for phaeochromocytoma in childhood is excellent.

Phaeochromocytomas in the National Registry of Childhood Tumours 1971-2002

Registration of non-malignant tumours has clearly been incomplete, especially before 1981.
Detailed data therefore only cover the period 1981-2000 only.

Table 1. Numbers of Registrations by Calendar Period and Tumour Behaviour

	Benign & Unspecified	Malignant	Total
1971-1980	6	2	8
1981-1990	11	4	15
1991-2002	20	1	21

(unspecified are regarded as benign in ICD-O).

Table 2. Numbers of Registrations by Age and Sex 1981-2002.

	0-4year	5-9year	10-14year	Male	Female	Total
Benign & Unspecified	1	13	17	19	12	31
Malignant	0	2	3	3	2	5

Phaeochromocytoma was more common in older children, with boys more frequently affected (1.5:1).
Incidence of malignant phaeochromocytoma was 0.02 per million children.
For benign and unspecified, a minimum estimate of incidence is 0.11 per million.
Among 31 children with benign or unspecified tumours, 3 were diagnosed post mortem; no other deaths have been recorded.
Of 5 children registered with malignant phaeochromocytoma, 2 died at intervals of 2 days and 14 months after diagnosis; the other 3 are alive with survival times between 3 and 22 years.

4.3 Presentation [1-5]

Most children present with a variety of non-specific symptoms including:
- hypertension, which may be intermittent,
- paroxysmal symptoms (e.g. headaches, fainting episodes, palpitations),
- abdominal pain.
- diarrhoea and other gastrointestinal symptoms.

Or more rarely (15%):
- with an incidental mass, usually identified on routine scanning, but occasionally intraoperatively for an unrelated condition.
- identified from a suggestive family history or clinical screening in a predisposed kindred (VHL, SDH, MEN 2, NF-1).

4.4 Statement of Best Practice

All patients with a suspected or confirmed diagnosis of phaeochromocytoma should be referred without delay to a regional specialist paediatric endocrine and UKKCSG centre familiar with the management of this condition and with appropriate medical and specialist surgical expertise.

All patients should be managed by a multidisciplinary team with experience in managing phaeochromocytoma. Liason between paediatric and adult specialities is very important.

Lifelong follow up is mandatory.

4.5 Diagnostic Investigations [2, 6, 7, 8]

i. Clinical

Where there is clinical suspicion of a phaeochromocytoma, a detailed family history and clinical examination for the physical characteristics of the following familial syndromes should be undertaken.

Neurofibromatosis Type 1 (NF-I)

- Café au lait patches >1.5 cm in diameter (numeric threshold depends upon age)
- Axillary freckling
- Neurofibromas
- Leisch nodules of iris
- Macrocephaly

Multiple Endocrine Neoplasia Type 2B (MEN2B)

- Marfanoid habitus
- Ganglioneuromatosis of bowel
- Neuromas of tongue and lips
- Hyperplasia of nerves of conjunctiva

Multiple Endocrine Neoplasia Type 2A (MEN 2A)

- Thyroid Mass
- Hirschsprung's disease
- Cutaneous lichen amyloidosis

Von Hippel Lindau (VHL) (major features)

- Retinal haemangiomas
- CNS haemangioblastoma (mainly cerebellar)
- Renal carcinoma (usually in adult life)

Familial Paraganglioma syndrome

- Paragangliomas - head and neck, thoracic, abdominal, pelvic

ii. Biochemical

Patients with suspected or confirmed phaeochromocytomas should be referred without delay to a specialist centre for further investigations and assessment.

The diagnosis of a phaeochromocytoma should be confirmed by measurement of at least two 24h urine samples for metanephrines (normetanephrine or metanephrine) and catecholamines (adrenaline, noradrenaline and dopamine). Phaeochromocytoma is diagnosed in more than 95% cases when both catecholamines and metanephrines are measured. A minimum of two negative 24h samples is required to rule out phaeochromocytoma. Urinary catheterisation may be necessary for adequate sampling.

24h urinary collection for measurement of VMA and HMMA should be undertaken to exclude a diagnosis of suspected neuroblastoma.

Medications administered during the urine collection, including antihypertensive therapy, should be discussed with clinical chemistry and if necessary stopped prior to collection to prevent misdiagnosis.

If the diagnosis of phaeochromocytoma is in doubt, the measurement of fractionated plasma metanephrines should be considered [9].

Stimulation tests are not recommended[10]. If the diagnosis is uncertain, referral to a unit with specific expertise in the management of phaeochromocytoma is advised.

iii. Imaging / Localising Investigations [2, 5, 8, 11-14]

Localising investigations should not be performed until a biochemical diagnosis has been made.

Abdominal ultrasound, looking for adrenal and retroperitoneal masses, can be carried out prior to cross-sectional imaging and may help direct future radiological studies.

Abdominal MRI or CT and a whole-body diagnostic MIBG scan (^{123}I) are advised.

MIBG in isolation is not a diagnostic investigation for phaeochromocytoma but can assist in detecting extra-adrenal or multiple synchronous primaries undetected by cross-sectional imaging.[6,14]

Further cross sectional imaging may be required if extra-adrenal abnormalities are demonstrated on an MIBG scan.

MIBG scans can miss small adrenal tumours, of particular relevance in familial disease.

Before undertaking an MIBG scan, potential drug interactions must be considered [13].

iv. **Other Localising Investigations**

Routine selective venous sampling for localisation is not required.

Under no circumstances should scan-directed or open biopsy be performed.

Other Tests

Blood should be taken for plasma:

- full blood count and haematocrit,
- urea and electrolytes,
- calcium and albumin,
- glucose [15],
- calcitonin (NB. a normal calcitonin does not exclude MEN 2 - *see MEN 2 chapter*)

Echocardiography and ECG if there is evidence of long-standing hypertension [16].
There is no need for preoperative staging [8, 17, 18].

4.6 Pre-Operative Medical Management

i. **Initial Stabilisation** [15, 19, 20]

Treatment with α adrenergic blockers

- α blockade would not normally have been started at the referring hospital. In cases of malignant hypertension, the tertiary centre should be consulted. Urgent consultation with the referring hospital should include advice about the dose.
- Phenoxybenzamine is generally recommended as the α adrenergic blocker of choice. *(See below for starting dose recommendations).* Doxazosin is an alternative.

Treatment with β adrenergic blockers

- β blockers, **if required**, should only be administered after full α blockade has been achieved.

ii. **Preparation for Surgery** [15, 19, 20]

Full α adrenergic blockade is mandatory before any surgical intervention.

α adrenergic blockade with phenoxybenzamine should be started at a dose of 0.1mg/kg 12-hourly.

The dose of phenoxybenzamine should be increased incrementally by 0.1 mg/kg/dose every 48 hours until postural hypotension is achieved. It is common at this stage for a child to complain of a stuffy nose. If phenoxybenzamine is poorly tolerated, doxazosin can be considered.

Adequate hydration is necessary to support the relatively reduced circulating blood volume resulting from α blockade.

β adrenergic blockade may be introduced **after** α adrenergic blockade has been achieved, to control tachycardia.

iii. **Anaesthesia** [21, 22]

The anaesthetist must be familiar with the complexities of the anaesthesia and closely involved with patient preparation.

Technical details are outside the remit of these guidelines.

4.7 Operative Management

This should be performed only by an appropriately trained and experienced adrenal surgeon, nominated by the centre for the management of paediatric phaeochromocytomas.

If removal of the left adrenal is planned, prophylactic immunisation should be considered in case of the necessity for splenectomy.

The preferred approach for resection is laparoscopic [23] but open resection is acceptable. If the designated paediatric surgeon is not familiar with the laparosocopic approach, it is appropriate to involve an adult endocrine surgeon fully experienced in laparoscopic adrenalectomy. There is no need for routine contralateral exploration or full laparotomy.

An incidentally discovered adrenal mass during an abdominal or retroperitoneal operation should not be disturbed. [24]

Even where there is a familial risk, prophylactic adrenalectomy is not indicated. [25]

If there are multiple synchronous tumours, the aim should be to remove all disease sites at the same time.

In children in whom bilateral adrenal involvement is suspected, bilateral adrenalectomy is usually recommended. [26]

The MDT may consider adrenocortical sparing in children to avoid the difficulties of corticosteroid replacement during adolescence.

At tumour removal or interruption of venous drainage, the anaesthetist should be alerted to stop anti-hypertensive therapy and prepare for the possibility of sudden profound hypotension.

4.8 Histopathology [1, 18, 27]

Malignancy cannot be excluded on histology.

Life-long follow up is advised in childhood phaeochromocytoma.

4.9 Postoperative Management

The child should be managed on a Paediatric Intensive Care or High Dependency Unit for the detection and management of early postoperative cardiac and circulatory instability.

Particular care is necessary to avoid postoperative hypoglycaemia [28] in the first 12 - 24 hours which can be fatal.

Post-operative haemorrhage may be a cause of hypotension.

Following bilateral adrenalectomy or bilateral adrenal tissue sparing surgery, glucocorticoid and mineralocorticoid steroid replacement therapy is necessary.

Urinary catecholamines and metanephrines should be re-checked 2 weeks post-operatively.

4.10 Malignant Phaeochromocytoma

Longterm survival has been reported but life expectancy is usually less than 5 years.

The treatment of choice is surgery for both the primary disease and any metastases. [18]

Unresectable tumours can be managed symptomatically with either phenoxybenzamine, doxazosin or α-methyltyrosine.

MIBG therapy [29] can be effective therapy either alone or in association with chemotherapy. [30]

The effectiveness of chemotherapy [31] alone has also been reported.

4.11 Short and Long Term Surveillance [31]

24 hour urinary catecholamines / metanephrines and measurement of blood pressure should initially be carried out 6-monthly. Closer postoperative screening may be advised if a higher risk of primary recurrence is suspected (eg after adrenocortical-sparing surgery). In the longer term, annual follow up may be adequate.

The adequacy of adrenocortical reserve should be tested postoperatively in children who have undergone adrenocortical sparing surgery.

The adequacy of substituted mineralocorticoid and glucocorticoid replacement therapy should be intermittently assessed in those who have undergone bilateral adrenalectomy.

If a recurrent or second primary phaeochromocytoma is suspected from raised catecholamines, the child should be investigated as for a new first presentation. If there was no genetic abnormality previously identified, the child should be referred back to the clinical geneticists.

Lifelong follow-up is required because of the propensity for contralateral tumours[27, 32].

4.12 Genetic Management [33, 34]

All children should be referred to the regional clinical genetics service.

A detailed family history should be taken, at least to third degree relatives. The absence of a family history does not preclude the patient having a mutation; childhood phaeochromocytoma is considered a probable genetic disorder requiring lifelong follow-up [27, 32]. Families with inherited susceptibility to phaeochromocytoma may show non-penetrance due to imprinting. It is important when taking the history to consider a diagnosis of :

- Neurofibromatosis type 1 (NF-1)
- Von Hippel Lindau [35] (VHL)
- Multiple Endocrine Neoplasia type 2 (MEN 2)
- Familial phaeochromocytoma and/or paraganglioma [36, 37]
- The Carney Complex + variant (genetic basis unknown) [38, 39]

Clinical examination for features of NF-1 should be carried out in the child and parents.

If a diagnosis is made from the family history or clinical examination, the appropriate genetic testing and family follow up should be carried out. Follow up for VHL, NF-1 and Carney Complex is outside the remit of these guidelines. MEN 2 is covered separately.

Blood should be taken for genetic studies after appropriate counselling (10mls in EDTA). This should be carried out where genetic counselling and family follow up are available.

Further investigation for those with genetic predispositions (ie calcitonin levels) should be guided by the genetic service *(see below)*.

Mutation analysis is mandatory in apparently sporadic childhood phaeochromocytomas; over 50% will have identifiable germline mutations. Germline mutations should be sought in the order of their frequency:

- von Hippel Lindau (VHL)
- Mitochondrial complex II mutation (SDH subunits B, C and D)
- RET (MEN 2)

A diagnosis of VHL is still possible without molecular confirmation. If genetic testing is negative, management should include:

- a specialist retinal examination
- consideration of an MRI/CT scan of the brain
- long term follow up.

Regular calcitonin screening is not necessary in children without a family history of MEN 2 and a negative RET gene analysis.

If a genetic abnormality is identified, long term follow up should be dictated by the genetic diagnosis. *(For MEN 2 refer to chapter 5, MEN 2 guidelines. For VHL refer to recommended VHL screening programmes.)*

4.13 Information and Support for Patients and Carers [40]

Support groups are available through "Contact a family" for patients with VHL and MEN syndromes.

The Neurofibromatosis Society provides support for families with NF-1.

Families may find useful information and contacts through **www.cancerbacup.org.uk**

4.14 Registration and Tumour Banking

All cases should be registered with the UKCCSG and links to familial cancer registries highlighted.

Consent to Tumour Banking - as per UKCCSG protocol- is encouraged .

CHAPTER FOUR

References

1. Medeiros LJ, Wolf BC, Balogh K, Federman M. Adrenal phaeochromocytoma: a clinico pathologic review of 60 cases. Hum Pathol 1985; 16:580-9.
2. Caty MF, Coran AG, Geogan M, Thompson NW. Current diagnosis and treatment of phaeochromocytoma in children. Arch Surg 1990; 125:978-981.
3. Ein SH, Pullerits J, Creighton R, Balfe JW. Pediatric Phaeochromocytoma. A 36-year review. Pediatr Surg Int 1997; 12:595-8
4. Revillon Y, Vaher P, Jan D, et al. Phaeochromocytoma in children: fifteen cases. J Pediatr Surg 1992; 27:910-1.
5. Ciftci AO, Tanyel FC, Senocak ME et al. Pheochromocytoma in children.J Pediatr Surg 2001; 36:447-452.
6. Gelfand MJ. Meta-iodobenzylguadinine in children. Sem Nucl Med 1993; 23:231-42.
7. Niccoll CD, Gerard SK. Diagnosis of phaeochromocytoma (letter). New Engl J Med. 1985; 312:721.
8. Deal J, Sever PS, Barratt TM, Dillon MJ. Phaeochomocytoma - investigation and mangement of 10 cases. Arch Dis Child 1990; 65:269-274.
9. Eisenhofer G, Lenders JWM, Lineham WM, Walther MM, Goldstein DJ, Keiser HR. Plasma normetanephrine and metanephrine for detecting phaeochromocytoma in von-Hippel-Lindau disease and multiple endocrine neoplasia Type 2. N Engl J Med 1999; 340: 1872-9
10. Remime WH, Chong GC, van Heerden J et al. Current management of phaeochromocytoma. Ann Surg 1994; 179:740-8.
11. Goldfarb DA, Novick AC, Bravo EL et al. Experience with extra adrenal phaeochromocytoma. J Urol 1989; 142:931-6.
12. Perel Y, Schlumberger M, Marguerite G et al. Phaeochromocytoma and paraglanglioma in children: a report of twenty-four cases of the French Society of Paediatric Oncology. Pediatr Hematol Oncol 1997; 14:413-22.
13. Shapiro B, Copp JE, Sisson JC, Eyres PL, Wallis J, Beierwaltes. Iodine - 131 meta-iodobenzylguanidine for the locating of suspected phaeochromocytoma: experience in 400 cases. J Nucl Med 1985; 26: 576-585.
14. Velchik M, Alavi A, Kresse LH. Localisation of phaeochromocytoma: MIBG, CT and MR corrolation. J Mucl Med 1989; 30:328-36.
15. Pullerits J, Ein S, Balfe JW. Anaesthesia for phaeochromocytoma. Can J. Anaesth 1988; 35:526-34.
16. Apgar V, Papper EM. Phaeochromocytoma: anaesthetic management during surgical treatment. Arch Surg 1951; 62:634.
17. Hume DM. Phaeochromocytoma in the adult and child. BJ Surg 1960; 99:458-96.
18. Ein SH, Weitzman S, Thorner P et al. Paediatric malignant phaeochromocytoma. J Pediatr Surg 1994; 29:1197-201.
19. Roizen MF. Endocrine abnormalities and anaesthesia. ASA Refresher Course Lectures 1985; pp 253.
20. Hill CJ. Phaeochromocytoma. Diagnosis, pre operative preparation and anaesthetic management. Br J Anaesth 1986; 58:1453-1458.
21. Roizen MF, Horrigan RW, Koike M et al. A prospective randomised trial of four anaesthetic techniques for resection of phaeochromocytoma. Anesthesiology 1982; 57:A43.
22. Desmonts JM, Marty J. Anaesthetic management of patients with phaeochromocytoma. Br J Anaesth 1984; 56:781-8.
23. Dudley NE, Harrison BJ. Comparision of open posterior vs. transperitonael laparoscopic adrenalectomy. Br J Surg 1999; 86:6562-60.
24. Samaan HA. Risk of operation in a patient with unsuspected pheochromocytoma. Br J Surg 1970; 57:462.

25. Albanese CT, Wiener ES. Routine total bilateral adrenalectomy is not warranted in childhood familial phaeochromocytoma. J Pediatr Surg 1993; 28:1248-52.
26. van Heerden JA, Sizemore GM, Carney JA, Grant CS, ReMine WH, Sheps SG. Surgical management of the adrenal glands in multiple endocrine neoplasia type two syndrome. World J Surg 1984; 8:612-21.
27. van Heerden JA, Roland CF, Carney JA, Sheps SG, Grant CS. Long-term evaluation following resection of apparently benign phaeochromocytoma(s)/paraganglioma(s). World J. Surg 1990; 14:325-329.
28. Costello GT, Moorthy SS, Vane DW, Dierdorf SF. Hypoglycaemia following bilateral adrenalectomy for phaeochromocytoma. Crit Care Med 1988; 16:562-3
29. Loh KC, Fitzgerald PA, Matthay KK, Yeo PP, Price DC. The treatment of malignant phaeochromocytoma with iodine-131 metaiodobenzylguanidine (131 I-MIBG) : a comprehensive review of 116 reported patients. J Endocrinol Invest 1997; 29: 648-58.
30. Sisson JC, Shapiro B, Shulkin BL, Urba S, Zempel S, Spaulding S. Treatment of malignant phaeochromocytoma with 131-J metaiodobenzylguanidine and chemotherapy.Am J Clin Oncol 1999:22:364.
31. Auerbach SD, Steakley LS, Young RC et al. Malignant phaeochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine and dicarbazine. Internal Med 1988; 109:267-273.
32. Ein SH, Shandling B, Wesson D et al. Recurrent phaeochromocytomas in children. J Pediatr Surg 1990; 25:1063-5.
33. Neumann H, Bausch B, McWinney SR, Bender BU, Gimm O, Franke G, Schipper J, Klisch J, Altehoeffer C, Zerres K, Januszewicz A and Eng C. Germline mutations in nonsyndromic phaeochromocytoma. N Engl J Med 2002; 346:1459-1466.
34. Oosterwijk JC, Jansen JC, van Schothorst EM, Oosterhof AW, Devilee P, Bakker E, Zoeteweij MW and van der Mey AGL. First experiences with genetic counselling based on predictive DNA diagnosis in hereditary glomus tumours (paragangliomas) J Med Genet 1996; 33:379-383.
35. Maher ER, Yates JR, Harries R, Benjamin C, Harris R, Moore AT, Ferguson- Smith MA. Clinical features and natural history of von Hippel Lindau disease. Q J Med 1990; 77: 1151-63.
36. Baysal BE. Hereditary paraganglioma targets diverse paraganglia. J Med Genet 2002; 39 : 617-622,.
37. Levine C, Skimming J, Levine E. Familial phaeochromocytomas with unusual associations. J Pediatr Surg 1992; 27:447-51.
38. Carney JA. Gastric stromal sarcoma, pulmonary chondroma, and extra adrenal paraganglioma (Carney triad): natural history, adrenocortical component, and possible familial occurrence. Mayo Clin Proc 1999; 74: 543-52.
39. Carney JA, Stratakis CA. Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet 2002; 108:132-9,
40. Confidential Enquiry into counselling for genetic disorders by non-geneticists: general recommendations and specific standards for improving care. British Journal of Obstetrics and Gynaecology 1999; 106: 658-663

CHAPTER FIVE

Chapter 5 - Medullary Thyroid Carcinoma (MTC) & Multiple Endocrine Neoplasia Type 2 (MEN 2) Syndromes

Main Issues

Medullary thyroid carcinoma (MTC) in childhood and adolescence occurs in individuals who have a genetic susceptibility, Multiple Endocrine Neoplasia type 2 (MEN 2). It may present as a solitary or dominant thyroid nodule, or within a diffuse or multinodular goitre in the euthyroid child.

MEN 2 is an autosomal dominant condition characterised by susceptibility to C-cell hyperplasia, MTC, phaeochromocytoma and in MEN 2A, tumours of the parathyroid glands. The condition is rare and affects about 1 per 50,000 individuals.

There are three separate subtypes of genetic susceptibility to MTC all caused by mutations in the RET tyrosine kinase receptor; MEN 2A and MEN 2B and familial medullary thyroid carcinoma (FMTC). The three subtypes differ in their age at presentation and in the spectrum of tumours which occur.

Only MEN 2A and MEN 2B present in childhood. There are marked genotype-phenotype correlations which help in determining patient and family management. Transformation from C-cell hyperplasia to invasive MTC and subsequent lymph node metastasis occurs early in MEN 2B.

It is noteworthy that the first manifestation of MEN 2 may be non-endocrine related to symptoms caused by colonic dysfunction (eg Hirschsprung's or ganglioneuromatosis).

Main recommendations

All euthyroid children with thyroid enlargement should be referred to a tertiary paediatric endocrinologist linked to a UKCCSG centre for assessment and exclusion of a potential malignant lesion which may even exist within a diffuse or multinodular goitre.

The importance of diagnosing MEN 2 cannot be over emphasised. Its purpose is :
- to confirm or exclude a synchronous phaeochromocytoma in a child with MTC, by the pre-operative measurement of 24 hr urinary fractionated catecholamines and metanephrines,
- to screen family members for the RET gene mutation thereby allowing prophylactic thyroidectomy in early childhood to prevent MTC,
- to prevent morbidity from phaeochromocytoma and hyperparathyroidism and MTC in family members.

Given the above, pre-operative diagnosis of MTC is desirable in euthyroid children presenting with a thyroid swelling. This requires a detailed and complete family history, basal calcitonin measurement and, if possible, a fine needle aspiration (FNA).

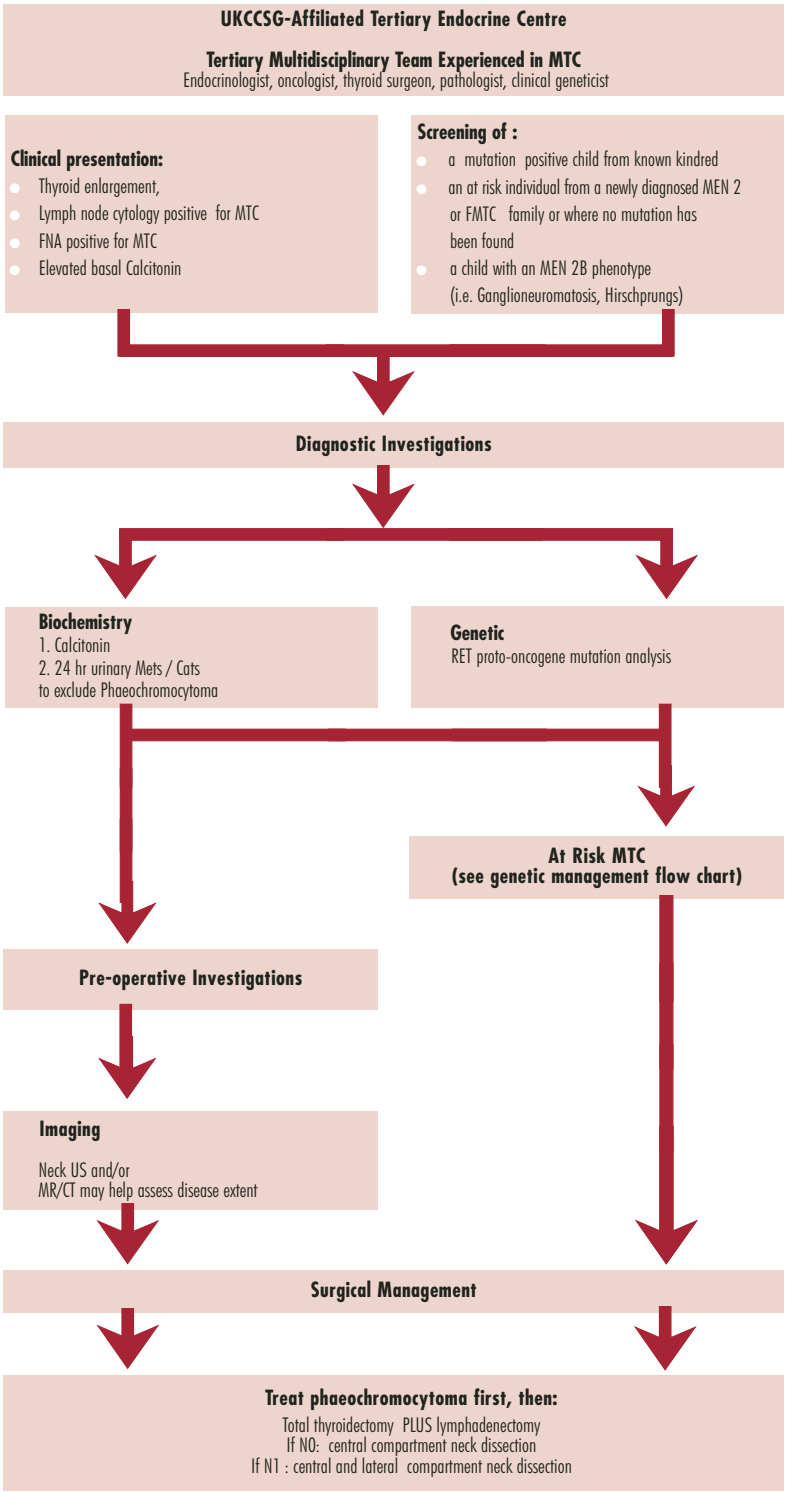
A clearly structured multidisciplinary (MDT) approach with family registration is essential to achieve optimal care, particularly for the lifelong follow-up required.

To avoid under or over- treatment, the MDT should clearly define whether a proposed surgical intervention is prophylactic or therapeutic. This will be determined by a combination of the MTC genotype, the age of the patient, the basal calcitonin level and the clinical findings.

It is recommended that all surgery for MTC (primary and recurrent) should be carried out by a surgeon experienced in the treatment of this disease and nominated by the cancer centre.

All patients with suspected or proven MEN 2 should be referred for genetic counselling and mutation analysis to the regional centre.

Recommended Flow Pathway for the Patient Presenting with Suspected Medullary Thyroid Carcinoma (MTC)



CHAPTER FIVE

5.2 Introduction and UK Registry Data

In childhood, MTC occurs almost exclusively as part of MEN 2. MEN 2 is an autosomal dominant condition characterised by susceptibility to medullary thyroid carcinoma (MTC), C-cell hyperplasia phaeochromocytoma and in MEN 2A, hyperparathyroidism. The condition is rare and affects about 1 in 50,000 individuals.

Germ line mutations of the RET proto-oncogene, are associated with three distinct variants of inherited susceptibility to MTC-MEN 2A, MEN 2B and familial medullary carcinoma (FMTC). They differ in the age at presentation and spectrum of tumours which occur. Only MEN 2A and MEN 2B present in childhood. There are marked genotype-phenotype correlations between the groups which direct patient and family management [1,2,3,4,5].

The importance of diagnosing MEN 2 cannot be over emphasised. Its purpose is to confirm or exclude a synchronous phaeochromocytoma prior to surgery for MTC, to screen family members for the RET proto-oncogene mutation and thereby permit prophylactic thyroidectomy, and to prevent morbidity from phaeochromocytoma, hyperparathyroidism and MTC. A multidisciplinary approach, formal organisation and family registration with the UKCCSG national registry for childhood tumours are essential.

The first manifestation of the disease may be non-endocrine (e.g. colonic dysfunction/megacolon due to ganglioneuromatosis in MEN 2B or Hirschprung's disease in MEN 2A [6,7,8]).

The absence of a family history of MTC or MEN 2 does not exclude genetically determined disease. The child may be the index case.

Thyroid Cancer in National Registry of Childhood Tumours 1971-2002

Table 1 Numbers of Registrations by Tumour Histology and Sex (1971-2002)

	Total	Male	Female	0-4 years	5-9 years	10-14 years
Total	194	58	136	7	36	151
Differentiated	146	42	104	2	28	116
Anaplastic	1	0	1	0	0	1
Medullary	47	16	31	5	8	34

Medullary carcinoma accounts for 24% thyroid cancers in national childhood registry. Girls accounted for 66% of medullary carcinoma, with relatively little variation by age group.

Table 2 Actuarial Survival (1971-2002)

Survival (years)	Percent surviving (%)
3	100
5	94
10	92
15	76
29	52

All deaths among cases of medullary carcinoma were from thyroid carcinoma and/or some other component of MEN.
NB. No deaths have yet been recorded among patients with medullary carcinoma diagnosed since 1990.

5.3 Presentation

MTC can occur in four clinical settings:

- Sporadic
  - rare in childhood.
- Familial
  - as part of MEN 2A
  - as part of MEN 2B
  - as part of FMTC - usual presentation in adulthood

Children with MTC may present:

- with a thyroid nodule, either solitary or within a goitre, or with lymph node enlargement. The cytology of MTC is characteristic and should prompt a specific diagnosis.
- on clinical screening of a child with a RET mutation from a known MEN 2 family,
- on clinical screening of an at-risk individual from a newly diagnosed MEN 2 or FMTC family, or where no mutation has been found,
- on clinical screening of a child with an associated MEN 2 phenotype (i.e. Ganglioneuromatosis, Hirschsprung's disease).

5.4 Statement of Good Practice

All euthyroid children with thyroid enlargement should be referred to a tertiary paediatric endocrinologist linked to a UKCCSG centre for assessment and exclusion of a potential malignant lesion which may even exist within a diffuse or multinodular goitre.

All children and adolescents with MTC should be investigated and managed by a designated multidisciplinary team in a tertiary endocrine and UKCCSG centre. The members should include a thyroid surgeon nominated by the cancer centre and experienced in MTC, an endocrinologist, oncologist, clinical geneticist and pathologist.

All patients should be referred for genetic counselling to the regional genetics centre.

5.5 Investigations

i. Biochemistry

Basal calcitonin prior to any treatment.

Phaeochromocytoma should be excluded prior to any surgical intervention by the measurement of 24 hr urinary fractionated catecholamines and metanephrines. [9,10]. The additional measurement of plasma fractionated metanephrines and normetanephrines increases the diagnostic yield [11,12].

ii. Thyroid Cytology

Preoperative diagnosis by FNA can be obtained in older children.

iii. Diagnostic Imaging

Neck ultrasound may demonstrate abnormal thyroid morphology and lymph node metastases.

MRI or CT is not mandatory prior to surgery but may be useful to assess the extent of local or systemic disease.

5.6 Management

If a phaeochromocytoma is diagnosed pre-operatively this should be surgically treated before embarking on thyroid surgery.

i. Preparation for Thyroid Surgery

Preoperative laryngoscopy is good practice in the older child.

Parents/carers, and the children themselves where appropriate, must be fully informed of the implications and increased risks of hypoparathyroidism and recurrent or superior laryngeal nerve injury after more radical thyroid surgery and lymph node dissection. Other complications include:

- the surgical scar,
- the possibility of lifelong thyroxine supplements,
- post-operative haemorrhage and return to theatre,
- voice change, breathing or swallowing difficulty consequent to temporary or permanent damage to the recurrent or superior laryngeal nerves,
- hypocalcaemia which may be temporary or permanent requiring treatment with calcium and/or vitamin D supplements.

ii. Surgical Treatment of MTC

It is recommended that surgery should only be carried out by a nominated surgeon within the cancer network, experienced in the treatment of MTC.

In the absence of palpable/pathological lymph nodes prior to surgery (N0), the recommended surgical intervention is total thyroidectomy and central neck compartment node dissection. However, children less than 10 years of age with T1 tumours and RET mutations affecting codons 630 and 634 can be managed without lymphadenectomy [13,14]. In the presence of palpable/pathological lymph nodes (N1) in the central compartment, confirmed by frozen section if necessary, bilateral, lateral compartment neck dissection should be performed .

Thyroidectomy should minimise the risk of avoidable injury to the recurrent and superior laryngeal nerves and attempt to conserve functioning parathyroid tissue. If preoperative investigations have demonstrated associated hyperparathyroidism, enlarged glands should be removed at the time of thyroid exploration.

iii. Post-Operative Management

Facilities and a written protocol must be available for the management of airway obstruction or wound haemorrhage after surgery.

Hypocalcaemia occurs after total thyroidectomy and lymph node surgery more frequently than after total thyroidectomy alone. Serum calcium should be measured at 4 hours post-operatively and then 12 hourly for 24-48 hours. Oral calcium supplementation should be commenced if the corrected serum calcium levels fall below 2mmol/l. At corrected serum calcium below 1.9mmol/l, slow intravenous calcium infusions should be administered.

Where hypocalcaemia persists beyond the first 48 post-operative hours, PTH levels should also be measured and Vitamin D supplementation added (alfacalcidol or calcitriol). The child should not be discharged until the calcium level is stable without the need for intravenous calcium administration in the preceding 24 hours.

It is good practice to assess the voice/vocal cord mobility after surgery by referral to a paediatric ENT surgeon.

Replacement with thyroxine is required. Suppressive doses of thyroxine are not necessary and thyroglobulin is **not** used as a tumour marker in patients with this type of thyroid cancer.

5.7 Staging

pTNM staging (AJCC, fifth edition, 1997) for MTC

	Primary Tumour
pT0	no evidence of primary tumour
pT1	Intrathyroidal tumour, <1 cm in greatest dimension
pT2	Intrathyroidal tumour, > 1cm to 4 cm in greatest dimension limited to thyroid
pT3	Intrathyroidal tumour, > 4 cm in greatest dimension limited to thyroid
pT4	Tumour of any size extending beyond the thyroid capsule
pTX	Primary tumour cannot be assessed
	Regional Lymph Nodes (cervical and upper mediastinal)
NX	regional nodes cannot be assessed
N0	no regional lymph node metastasis
N1	regional lymph node metastasis
	● N1a metastasis in ipsilateral cervical nodes
	● N1b metastasis in bilateral, midline or contralateral cervical or superior mediastinal nodes
	Distant Metastases
MX	distant metastases cannot be assessed
M0	no distant metastasis
M1	distant metastasis

5.8 Persistent / Recurrent Calcitonin Elevation

Although there is good evidence that meticulous initial surgery will reduce the risk of postoperative calcitonin elevation, high calcitonin levels after surgery are common. The frequency of this finding will depend upon the pre-operative basal calcitonin[15], the stage of the tumour at presentation and the extent of initial surgery.

It is important to distinguish loco-regional persistent or recurrent disease from distant micro or macro metastases. Non-invasive imaging (chest CT or MRI and cervical and/or abdominal ultrasound) performed to distinguish loco-regional recurrence from distant metastases as the source of calcitonin excess, may not be helpful.

Cross-sectional imaging understages metastatic MTC because of its morphological pattern in lung and liver (i.e. miliary nodular disease). In adults, laparoscopy to assess the liver and selective venous sampling and / or arteriography will in some cases identify occult military MTC. Other less invasive options to detect metastatic MTC in patients with rising calcitonin and negative whole body CT or MRI, include pentavalent DMSA, MIBG, indium-labelled octreotide scans, and FDG-PET CT. In general functional isotope studies are most likely to detect bulk disease.

True local recurrence is unusual after adequate initial surgery. Re-operation on the neck (lymphadenectomy of the central and/or lateral compartments) with curative intent when initial surgery was inadequate, should be considered if there is no evidence of distant disease.

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

Re-operative surgery should also be considered even when there are known distant metastases to prevent the complications of bulk disease affecting the airway, oesophagus or laryngeal nerves.

Such cases because of their rarity, should be discussed with an endocrine surgeon experienced in the treatment of MTC to decide whether or not there is an indication to proceed with re- operative surgery.

5.9 The Clinical Genetic Management of MTC and MEN 2

i. **Family History**

A family history of any benign or malignant tumours, to include at least 1st, 2nd and 3rd degree relatives, should be taken.

Table 3. Features of Familial MTC Syndromes

	Endocrine Features	Non Endocrine features
MEN 2B	MTC (100%) Phaeochromocytoma (>50%)	Marfanoid habitus Ganglioneuromatosis of bowel Neuromas of tongue and lips Hyperplasia nerves of conjunctiva
MEN 2A	MTC (100%) Parathyroid hyperplasia or adenoma (10-20%%) Pheochromocytoma (50%)	Hirschsprung's disease Cutaneous lichen amyloidosis
FMTC	MTC (adult onset)	

ii. **Molecular Genetic Testing** *(see flow chart Page 104)*

a. **MTC**

Mutation analysis of the RET gene is mandatory in children with MTC. It should be carried out in an environment where individuals and families can receive appropriate genetic counselling and follow-up [16].

Mutations in RET are identifiable in about 98% of MEN 2 patients.

Most mutations are in exons 10, 11, 13, 14 & 15, which should be routinely screened.

MEN 2A is most frequently caused by mutations at 634 Cys. MEN 2B is caused by a mutation at codon 918 in more than 95% of patients and codon 883 is the next most common alteration.

Any child presenting with MTC and negative on the routine screen, should have the other exons screened for mutations.

b. **Children at Risk of MTC** [1,17]

Children will be at risk either because they come from a known MEN 2 kindred or have been identified with an associated MEN 2 phenotype.

- **MEN 2 <u>Family with a known RET mutation</u>**

- Predictive testing of the at-risk child should be carried out by mutation analysis
- Children who have not inherited the mutation do not have the disease. No other screening is required
- Children with the mutation and raised basal calcitonin - treat as MTC *(see a)* above
- Children with the mutation and with normal basal calcitonin require prophylactic total thyroidectomy which should be performed in:
- MEN 2B within the first year [18]
- MEN 2A around the age of 2-5 years [14,19,20]

NB. Phenotype-genotype correlations which may influence the age at recommended surgery are emerging, and the most recent information should be sought from the MDT clinical geneticist [14,21,22]

MEN 2 Family with unknown mutation

Linkage Analysis

- Linkage analysis may be used in families with a secure clinical diagnosis of MEN 2 where no mutation is detected.
- Where possible, predictive testing with linked markers (intragenic or flanking) should be undertaken;
- Children who have inherited the low risk flanking markers or intragenic marker do not have the disease. No other screening is required.
- Children who have inherited the high risk marker(s) treat as children who have inherited the mutation *(see above a)*.

Families Unsuitable for Linkage Analysis

- These patients should undergo biochemical screening from the age of two years.
- raised basal calcitonin, treat as MTC (see a) above,
- normal basal calcitonin, proceed to pentagastrin test,
- normal basal calcitonin, and positive pentagastrin test, treat as having a RET mutation and proceed to age- and disease-appropriate prophylactic thyroidectomy
  N.B. there is a 5% false positive and false negative rate for this test [23]
- normal basal calcitonin and normal pentagastrin test, repeat screen 1-2-yearly until 40 years of age [1]

Associated Phenotypes: Ganglioneuromatosis, Hirschsprung's Disease [6,8,24,25]

A detailed clinical examination and family history is required.

a. Ganglioneuromatosis

Children presenting with megacolon and biopsy proven ganglioneuromatosis require a basal calcitonin and mutation analysis at codon 918 and 883 to exclude MEN 2B

A patient with megacolon and rectal biopsy findings of ganglioneuromatosis and an MEN 2B mutation (codon 918, 883) should be managed as MEN 2B *(see above)*.

- Patients with ganglioneuromatosis but without an MEN 2B mutation require estimation of a basal calcitonin.
- If the calcitonin level is elevated, further molecular and clinical assessment is required. Treat as MEN 2B.
- If the initial basal calcitonin and subsequent annual stimulated calcitonin levels remain normal, by 10 years of age the family may be reassured.

b. **Hirschsprung's Disease**

In children presenting with Hirschsprung's disease mutation analysis of exon 10 should be considered as mutations at codon 609, 618 or 620 occur in Hirschsprung's disease with MEN 2A [24,25.]

If an exon 10 mutation at codon 609, 618, or 620 is identified, the child and other individuals in the family with the mutation should be managed as MEN 2A and undergo age-appropriate prophylactic thyroidectomy.

iii. **Prophylactic Thyroid Surgery for MEN2 / FMTC**

The aim is to carry out an age-appropriate prophylactic total thyroidectomy in all patients with MEN 2 / FMTC and prevent the subsequent development of MTC.

To avoid under or over- treatment, the MDT should clearly define whether a proposed surgical intervention is prophylactic or therapeutic. This will be determined by the combination of the MTC genotype, the age of the patient, the calcitonin level and the clinical findings.

In patients less than 10 years of age undergoing **prophylactic** thyroidectomy for MEN 2A, it is probably unnecessary to perform lymph node dissection[13 14]. In older children and those with MEN 2B, central compartment lymphadenectomy should be performed. In patients with FMTC, lymph node dissection is not indicated under the age of 20 years[13].

Where the mutation is identified in the older child, it is important to remember that MTC may already be present and thus therapeutic, rather than prophylactic surgery may be necessary. In such cases preoperative investigations are required as for MTC. *(see above).*

Thyroidectomy should minimise the risk of avoidable injury to the recurrent or superior laryngeal nerves and attempt to conserve functioning parathyroid tissue. If preoperative investigations have demonstrated associated hyperparathyroidism, enlarged glands should be removed at the time of thyroid exploration.

5.10 Long Term Follow Up of Patients with MTC or MEN 2 Syndromes

Serum calcitonin should be checked at 2 - 3 post-operative months and at subsequent visits 6-monthly, even in patients who have undergone prophylactic surgery[14] .

CEA can be measured as an additional tumour marker.

Persistently raised basal calcitonin levels after surgery indicate residual local or systemic disease, even in cases with apparently curative surgery. Normal calcitonin levels after surgery do not exclude residual disease.

A clearly structured multidisciplinary (MDT) approach with family registration is essential to achieve optimal care, particularly for the lifelong follow-up required:

- post-operative follow-up of MTC
- in MEN 2A and MEN 2B, a 24hr urinary collection for metanephrines and catecholamines should be measured annually to exclude a phaeochromocytoma. [26,27]
- annual measurement of calcium and PTH should be undertaken in MEN 2A families [28]

(for subsequent management see chapter 6, hyperparathyroidism section)

CHAPTER FIVE

5.11 Information and Support for Patients and Carers

All patients should be offered genetic counselling.

Patients may find the following websites and contact organisations helpful:

- AMEND: Association for Multiple Endocrine Neoplasia Disorders
  www.amend.org.uk
- British Thyroid Foundation, PO Box 97, Clifford, Wetherby, West Yorkshire LS23 6XD
  www.btf-thyroid.org
- MEN Society Canada, Box 100, MEOTA, Saskatchewan, Canada SOM 1XO

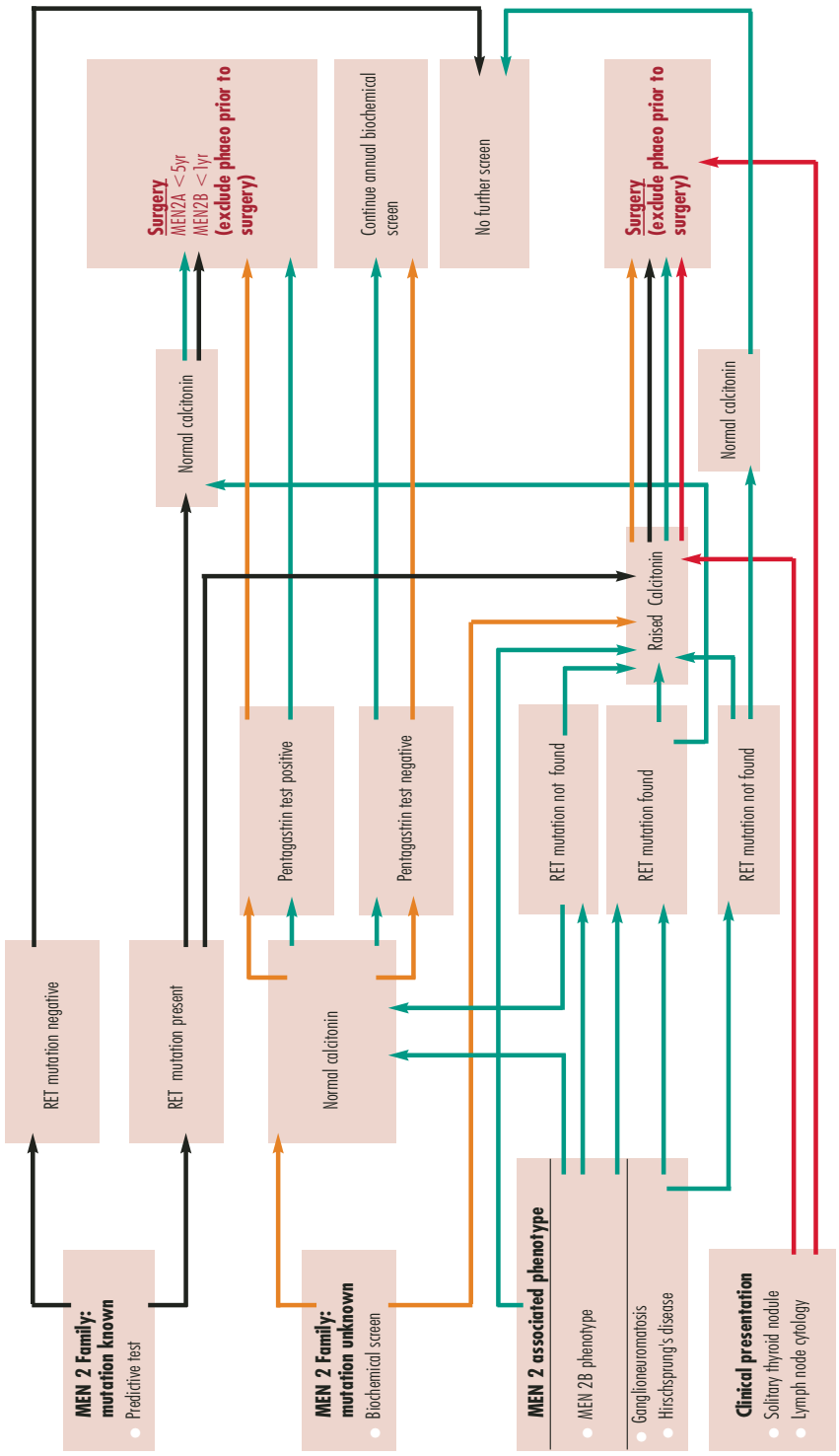
5.12 Registrations and Tumour Banking

All patients and their families should be registered with the UKCCSG by their paediatric oncologist or endocrinologist.

Regional genetic centres/registries should also be informed and their notification highlighted in the UKKCSG form.

Tumour Banking according to the UKCCSG protocol is encouraged .

The Clinical Genetic Management of Children with MTC and MEN 2 Syndromes and their Families



CHAPTER FIVE

References

1. Brandi, M.L., Gagel, R.F., Angeli, A., et al. Consensus.Guidelines for Diagnosis and Therapy of MEN Type 1 and Type 2. J Clin Endocrinol Metab 2001; 86:5658-5671.
2. Carling T. Multiple Endocrine Neolasia syndrome: genetic basis for clinical management. Current Opinion in Oncology 2005; 17(1): 7-12,.
3. Marx SJ. Molecular Genetics of Multiple Endocrine Neoplasia Types 1 and 2. Nature Reviews Cancer 2005; 5: 367-375,.
4. Thakker RV. Multiple Endocrine Neoplasia. Horm Res 2001;.56 (suppl 1): 67-72.
5. Eng, C. Multiple endocrine neoplasia type 2 and the practice of molecular medicine. [Review] [64 refs]. Reviews in Endocrine & Metabolic Disorders 2000; 1:283-290.
6. Smith, V.V., Eng, C. and Milla, P.J. Intestinal ganglioneuromatosis and multiple endocrine neoplasia type 2B: implications for treatment. Gut 1999; 45:143-146,
7. Leboulleux, S., Travagli, J.P., Caillou, B., et al. Medullary thyroid carcinoma a part of a multiple endocrine neoplasia type 2B syndrome. Cancer 2002; 94:44-50.
8. Decker, R.A., Peacock, M.L. and Watson, P. Hirschsprung disease in MEN 2A: increased spectrum of RET exon 10 genotypes and strong genotype-phenotype correlation. Human Molecular Genetics 1998; 7:129-134.
9. Orchard T, Grant CS, van Heerden JA, Weaver A. Pheochromocytoma–continuing evolution of surgical therapy. Surgery.year 114(6):1153-8; and discussion 1158-9, .
10. Sheps SG, Jiang NS, Klee GG. Diagnostic evaluation of pheochromocytoma. Endocrinology and Metabolism Clinics of North America 1988; 17(2):397-414.
11. Eisenhofer G, Lenders JW, Linehan WM, Walther MM, Goldstein DS, Keiser HR. Plasma normetanephrine and metanephrine for detecting pheochromocytoma in von Hippel-Lindau disease and multiple endocrine neoplasia type 2. N Eng J Med 1999; 340(24):1872-9.
12. Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab 2003; 88(2):553-8,.
13. Machens A, Niccoli-Sire P, Hoegel J, et al European Multiple Endocrine Neoplasia (EUROMEN) Study Group. Early malignant progression of hereditary medullary thyroid cancer. N Engl J Med 2003; 349:1517-25.
14. Skinner MA, Moley JA, Dilley WG, Owzar K, Debendetti MK, Wells JR. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. N Engl J Med 2005; 353:1105-13. comment 1162-4
15. Machens A, Schneyer U, Holzhausen HJ, Dralle H. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. J Clin Endocrinol Metab 2005; 90 : 2029-34
16. Harris, R., Lane, B., Harris, H., et al. National Confidential Enquiry into counselling for genetic disorders by non-geneticists: general recommendations and specific standards for improving care. Br J Obs and Gynaecol 1999; 106:658-663.
17. Johnston, L.B., Chew, S.L., Trainer PJ, et al. Screening children at risk of developing inherited endocrine neoplasia syndromes. Clin Endocrinol 2000; 52: 127-136.
18. Gagel RF, Cote GJ, Martins Bugalho MJ, et al. Clinical use of molecular information in the management of multiple endocrine neoplasia type 2A. J Intern Med 1995; 238(4):333-41.
19. Pacini F, Romei C, Miccoli P, et al. Early treatment of hereditary medullary thyroid carcinoma after attribution of multiple endocrine neoplasia type 2 gene carrier status by screening for ret gene mutations. Surgery 1995; 118(6):1031-5.
20. Gill JR, Reyes-Mugica M, Iyengar S,et al. Early presentation of metastatic medullary carcinoma in multiple endocrine neoplasia, type IIA: implications for therapy. J Pediatr1996; 129(3):459-64.

21. Sanso, G.E., Domene, H.M., Garcia, R., et al. Very early detection of RET proto-oncogene mutation is crucial for preventive thyroidectomy in multiple endocrine neoplasia type 2 children: presence of C-cell malignant disease in asymptomatic carriers. Cancer 2002; 94:323-330.

22. Yip, L., Cote, G., Shapiro, S.E., et al. Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. Arch Surg 2003; 138:409-416.

23. Marsh D.J., McDowall D, Hyland, V.J., et al. The identification of false positive responses to the pentagastrin stimulation test in RET mutation negative members of MEN 2A families. Clin Endocrinol 1996; 44:213-220.

24. Borrego, S., Eng, C., Sanchez, B., Saez, M., Navarro, E. Antinolo, G. Molecular Analysis of the RET and GDNF Genes in a Family with Multiple Endocrine Neoplasia Type 2A and Hirschsprung disease. J Clin Endocrinol Metabolism 1998; 83:3361-3364.

25. Cohen, M.S., Phay, J.E., Albinson, C., et al. Gastrointestinal manifestations of multiple endocrine neoplasia type 2. Annal Surg 2002; 235:648-54; discussion 654-5.

26. Gagel RF, Tashjian AH Jr, Cummings T, Papathanasopoulos N, Kaplan MM, DeLellis RA, Wolfe HJ, Reichlin S. The clinical outcome of prospective screening for multiple endocrine neoplasia type 2a. An 18-year experience. N Engl J Med 1988; 318(8):478-84.

27. Gagel RF, Robinson MF, Donovan DT, Alford BR. Clinical review 44: Medullary thyroid carcinoma: recent progress. J Clin Endocrinol Metabol 1993;76(4):809-14.

28. Kraimps JL, Denizot A, Carnaille B, et al. Primary hyperparathyroidism in multiple endocrine neoplasia type IIa: retrospective French multicentric study. Groupe d'Etude des Tumeurs a Calcitonine (GETC, French Calcitonin Tumors Study Group), French Association of Endocrine Surgeons.1993. World Journal of Surgery 1996; 20(7): 808-12; discussion 812-3.

CHAPTER SIX

Chapter 6 - Hyperparathyroidism and Pituitary Tumours in Association with Multiple Endocrine Neoplasia Type 1 (MEN 1) Syndrome

6.1 Executive Summary

Main Issues

True hypercalcaemia is rare in childhood and adolescence; that due to underlying hyperparathyroidism is extremely rare.

Hyperparathyroidism occurring in this age group should be considered a genetically determined disease.

Primary hyperparathyroidism in children can be sporadic but is more often due to a genetic predisposition. A careful family history should be taken, with clinical and genetic investigation for associated conditions (MEN 1, MEN 2, hyperpararathyroidism / jaw tumour families).

Pituitary tumours may be the first presentation of the disease.

Management of patients with MEN 1 requires a specialist multidisciplinary team (MDT). Follow-up should be lifelong.

Main Recommendations

All patients with hypercalcaemia should have a plasma PTH measured .

Suspected or confirmed cases of primary hyperparathyroidism must be referred to a regional specialist paediatric endocrine and UKCCSG centre, with appropriate surgical and genetic expertise.

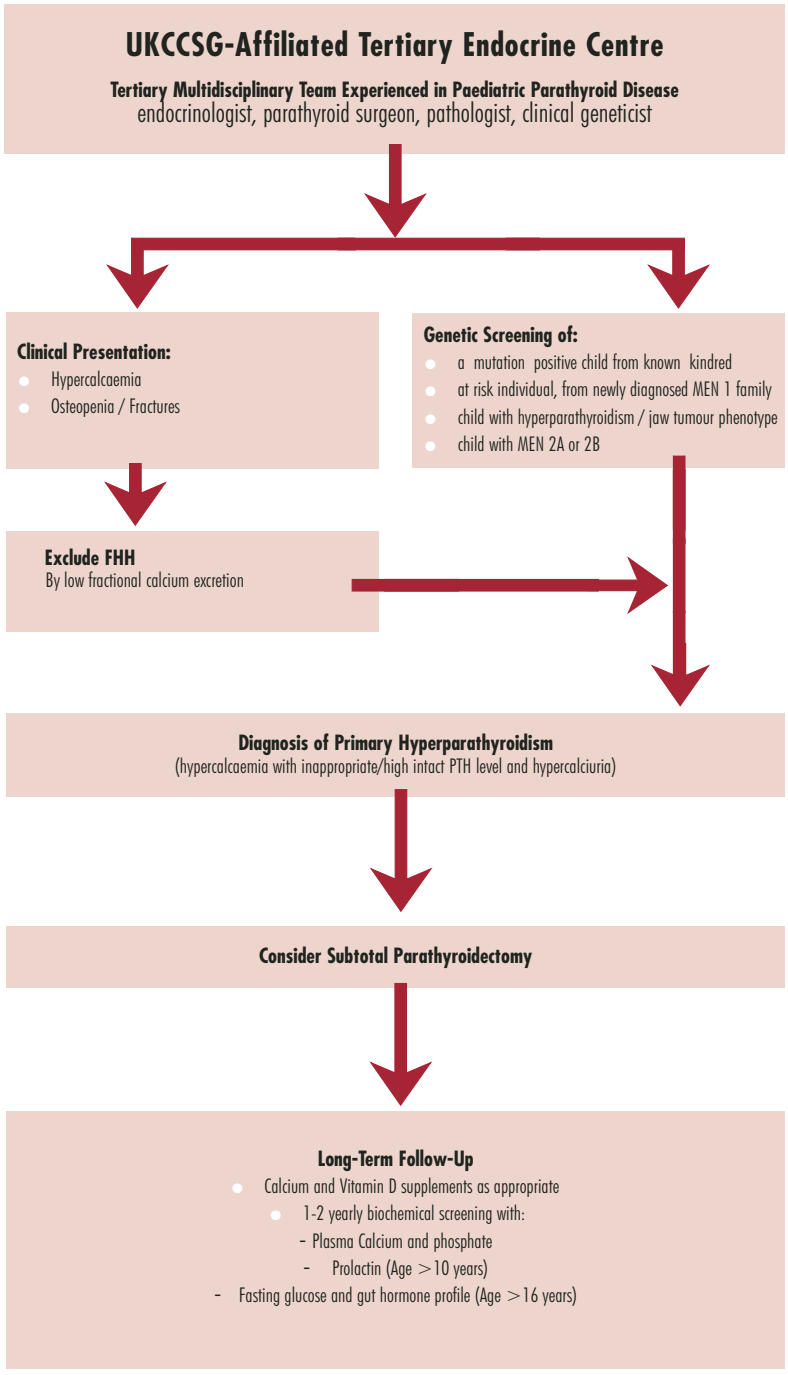
It is recommended that surgery for hyperparathyroidism (primary and recurrent) should be carried out by a surgeon experienced in the treatment of this disease and nominated by the centre's MDT.

Written guidelines must be available for the pre-operative management of hypercalcaemia.

All patients with hyperparathyroidism or pituitary tumours should be referred for genetic counselling and mutation analysis. Because of the increased risk of parathyroid carcinoma in individuals with parafibromin mutations, mutation analysis for the parafibromin gene should be undertaken in patients and families in which a MENIN mutation has not been detected, or in the presence of a parathyroid carcinoma.

With effect from the publication of these guidelines, cases of hyperparathyroidism should be registered with the UKCCSG.

Recommended Flow Path for the Management of Patients with Hypercalcaemia



CHAPTER SIX

Chapter 6A: Hyperparathyroidism and MEN 1 Syndrome

6A.1 Introduction and Registry Data

Hyperparathyroidism in childhood and adolescence should be considered a genetically determined disease [1,2].

- Familial hyperparathyroidism can occur as part of
- MEN 1 syndrome,
- MEN 2A syndrome,
- MEN 2B syndrome (rarely),
- Hyperparathyroidism/jaw tumour families
- An isolated autosomal dominant disorder,
- Severe neonatal hyperparathyroidism in patients who are homozygous for mutation of the calcium sensing receptor.

Children with hyperparathyroidism have not to date been included in the UK National Registry of Childhood Tumours. It has been agreed that, with effect from the publication of these guidelines, childhood cases of hyperparathyroidism and family registration with the UKCCSG National Registry of Childhood Tumours are essential.

6A.2 Presentation of Hyperparathyroidism

Symptomatic hyperparathyroidism is rare in childhood or adolescence.

Presentation in childhood often results from screening families at risk,[3] as an incidental finding or, after the long term follow-up of patients who have received cranio-cervical irradiation [4].

6A.3 Statement of Best Practice

Children and families with suspected or confirmed hyperparathyroidism, a clinical diagnosis of MEN 1, or those with a MENIN mutation, should be investigated and managed by a designated multidisciplinary team (MDT). The members should include an endocrinologist, an experienced parathyroid surgeon, a clinical geneticist, and pathologist in a UKKCSG centre with tertiary endocrine expertise.

6A.4 Investigations

i. Biochemistry

Hyperparathyroidism is classically associated with hypercalcaemia and a high or inappropriate high-normal intact PTH.

Normocalcaemic hyperparathyroidism can occur.

Urinary calcium:creatinine ratio is elevated in hyperpararthyroidism

Familial hypercalcaemic hypocalciuria (FHH) should be excluded by the absence of a relevant family history and the demonstration of a low urinary calcium:creatinine ratio.

ii. **Diagnostic Imaging**

Pre-operative localisation studies are not routinely indicated in children with hyperparathyroidism[5]. Preoperative localisation of abnormal parathyroid glands is least effective in multiglandular disease.

Supernumerary and/or ectopic parathyroid tissue occurs more frequently in familial disease.

Renal ultrasound screening for nephrocalcinosis may be considered as a baseline.

6A.5 Management

The indication for and timing of surgery in adult patients with mild hypercalcaemia or normocalcaemic hyperparathyroidism is controversial. The indication for and timing of surgery in childhood patients should be a matter for discussion between the patient and his/her family and the MDT. The latter should be familiar with the recommendations of the 2002 Workshop on "Asymptomatic Hyperparathyroidism"[6].

Severe or symptomatic hypercalcaemia and/or the presence of nephrocalcinosis are indications for surgical treatment.

i. **Preparation for Surgery**

a. **Treatment of Hypercalcaemia**

Written guidelines must be available for the pre-operative treatment of severe hypercalcaemia.

Severe (> 3 mmol/l) hypercalcaemia requires urgent treatment to prevent cardiac arrhythmia, hypotension and renal failure. Initial management is usually rehydration with normal saline and correction of any fluid deficits.

Persistent hypercalcaemia may require intravenous bisphosphonate (pamidronate) therapy administered carefully according to local protocols.

b. **Pre-operative assessment**

Preoperative laryngoscopy is good practice in the older child.

Parents/carers, and the children themselves where appropriate, must be fully informed of the implications and risks of operation. These include:

- the surgical scar,
- post-operative haemorrhage and return to theatre,
- voice change, breathing or swallowing difficulty consequent upon temporary or permanent damage to the recurrent laryngeal nerves,
- hypocalcaemia which may be temporary or permanent requiring treatment with calcium and/or vitamin D supplements,
- the possibility of persistent or recurrent hypercalcaemia.

ii. Surgery

Cervical exploration should only be performed by an experienced parathyroid surgeon with an understanding of the surgical strategy in patients with genetically determined disease. All four parathyroid glands should be identified.

The minimum intervention in patients with four-gland enlargement is subtotal parathyroidectomy, leaving a single gland remnant marked to facilitate subsequent re-exploration. Bilateral transcervical thymectomy should be performed.

An alternative surgical approach for patients with multiglandular disease is that of total parathyroidectomy and transcervical thymectomy, with forearm autograft and cryopreservation of the most normal excised parathyroid gland.

In patients with disease affecting fewer than four glands, the surgical strategy should be left to the judgement of the individual surgeon. Normal sized parathyroid glands should not be biopsied or removed, but marked with a non-absorbable suture to aid subsequent intraoperative identification if required.

iii. Post-Operative Management

Facilities and written guidelines for the post-operative management of airway obstruction, wound haemorrhage and hypocalcaemia must be available.

a. Calcium Homeostasis

Unlike in adults, hypocalcaemia may occur very early in children and calcium monitoring should commence within the first six post-operative hours.

Immediate postoperative hypocalcaemia is common after multiple gland resection and early calcium and vitamin D supplementation is required, according to local guidelines.

After subtotal parathyroidectomy or autotransplantation, calcium supplements and 1-alphacalcidol will be required for some weeks after surgery when treatment can be weaned according to local guidelines. Serum calcium levels at the lower limit of normal encourage recovery of the parathormone-calcium axis.

Patients having undergone **total** parathyroidectomy will require lifelong replacement with 1-alphacalcidol. Calcium supplements can usually be stopped once serum calcium is stable and within the normal range.

b. Persistent hyperparathyroidism

Persistent hyperparathyroidism after surgery is less likely in the most experienced hands . The further management of such a case will depend upon findings at initial surgery, the operation performed and the degree of hypercalcaemia. Further management requires careful consideration.

c. **Recurrent hyperparathyroidism**

Recurrent hyperparathyroidism in patients with genetically determined disease who have undergone subtotal parathyroidectomy is common (up to 50% at 5 yrs) [7, 8].

After surgery, follow-up in an endocrine unit which has provision for transitional care to an adult endocrine service is necessary for long-term follow-up.

d. **Parathyroid carcinoma**

Parathyroid carcinoma may occur in association with both MEN 1 and non-MEN familial hyperparathyroidism. In adults the presence of a high calcium and/or PTH or palpable tumour should raise the surgen's suspicions, but cases in children may only be confirmed by the pathologist after surgery. The treatment for parathyroid carcinoma includes thyroid lobectomy to reduce the risk of local recurrence.

e. **Medium to long term clinical surveillance**

This is necessary to exclude recurrent hyperparathyroidism and other manifestations of the disorder *(see 6A.6)*.

6A.6 Clinical Genetic Management of Children with Hyperparathyroidism and MEN-1 and their Families

i. **Family History**

Family history should be taken to include at least 1st degree, 2nd degree, and preferably 3rd degree relatives of affected individuals. Diagnosis of a familial disorder may be possible from the family history.

ii. **Familial Disorders**

a. **Multiple Endocrine Neoplasia Type 1 (MEN 1)** [9, 10, 11]

Multiple Endocrine Neoplasia type 1 (MEN1) is an autosomal dominantly inherited condition caused by mutations in the MENIN gene.

Its prevalence, reported at about 1 in 50,000, is under-ascertained.

Disease expression before 10 years of age is rare.

Hyperparathyroidism is the commonest (>90%) and usually earliest manifestation of the disease. Rarely in children, pituitary tumours (usually prolactinomas) may be the first manifestation of the disease. MEN 1 associated pancreatic islet cell disease, though serious is even more rare in children and outside the remit of these guidelines. Adrenocortical, carcinoid, facial angiofibromas, collagenomas and lipomatous tumours may be part of an MEN disorder.

Table 1. Clinical features suggestive of a diagnosis of MEN 1

Major Features	Minor Features
1. Hyperparathyroidism 2. Pancreatic neuroendocrine tumour ● Gastrinoma ● Insulinoma ● Non functioning ● Other 3. Anterior pituitary ● Prolactinoma ● Growth Hormone secreting ● Other	1. Adrenocortical tumours 2. Foregut derived carcinoid tumours ● Thymic ● Bronchial ● Gastric (non functioning) 3. Lipomas 4. Facial angiofibromas 5. Collagenomas 6. Phaeochromocytoma 7. Ependymoma

The following criteria are required for a diagnosis of MEN 1:

- an individual is diagnosed with tumours from two of the principal sites

or

- at least two individuals in a family have had one tumour from the principal sites

or

- a MENIN mutation is found in an atypical family - one major and one minor feature in an individual or relatives.

b. **Multiple Endocrine Neoplasia type 2A (MEN 2A)**

Hyperparathyroidism occurs in 25% patients with MEN 2A but does not usually occur as part of MEN 2B

c. **Hyperparathyroidism/ jaw tumour syndrome**

This is a rare dominantly inherited tumour susceptibility to parathyroid tumours caused by mutations in parafibromin on chromosome 1q25. It can present with hyperparathyroidism in adolescence and is associated with an increased risk of malignancy. Approximately one third patients also develop ossifying fibromas, primarily of the mandible and maxilla. Kidney cysts and hamartomas can occur [12].

d. **Autosomal Dominant Hyperparathyroidism**

Autosomal dominant hyperparathyroidism families without other features suggestive of MEN syndromes, have been found to have germline mutations in the MENIN gene whilst others have been found to have mutations in parafibromin. There is an increased risk of parathyroid carcinoma in individuals with parafibromin mutations[2]. Mutation analysis for the parafibromin gene should be undertaken in MENIN-gene mutation-negative patients and families, or in the presence of a parathyroid carcinoma.

e. **Severe Neonatal Hyperparathyroidism**

Severe neonatal hyperparathyroidism is a recessive disorder due to mutations in the parathyroid calcium sensing receptor gene. Heterozygotes have familial hypocalciuric hypercalcaemia (FHH). A family history is invariably present [13].

iii. **Genetic Testing**

This should be carried out in an environment where individuals and families can receive appropriate genetic counselling and follow-up[14].

a. **Genetic Testing of the Index Case**

MENIN gene mutation analysis

- Mutation analysis of the whole MENIN gene should be carried out in a child or adolescent with hyperparathyroidism even in the absence of a positive family history [15].
- A mutation in the MENIN gene will be detected in more than 80% of clinically diagnosed MEN 1 families and in about 60% of atypical families partially fulfilling diagnostic criteria for MEN 1[16, 17].
- Failure to detect a mutation in the MENIN gene does not exclude a diagnosis of MEN 1.

Parafibromin gene mutation analysis

- Children and adolescents with hyperparathyroidism and no detected mutation in MENIN, should have mutation analysis of parafibromin.
- Children and adolescents with parathyroid carcinoma or atypical parathyroid adenoma, and without family history of MEN 1, should have mutation analysis of parafibromin **prior** to MENIN testing[18, 19].
- Children and families with a combination of hyperparathyroidism and jaw tumours should undergo mutation analysis of parafibromin.
- Identification of mutations in parafibromin will permit predictive testing for other family members.

b. **Genetic Testing of the Kindred**

A predictive genetic test of at risk children from families with a known MENIN mutation should be offered prior to starting biochemical screening.

Those children identified with a MENIN mutation, or those refusing genetic testing, should undergo biochemical screening *(see 6A.7)*

Families fulfilling the diagnostic criteria for MEN 1 in which no MENIN mutation is found, can be tested using linked markers prior to biochemical screening. Those who have inherited the MEN 1 haplotype should undergo biochemical screening.

Children from families in which a MENIN mutation has not been identified but otherwise fulfil the diagnostic criteria for MEN 1 and are unsuitable for linkage analysis, should undergo biochemical screening.

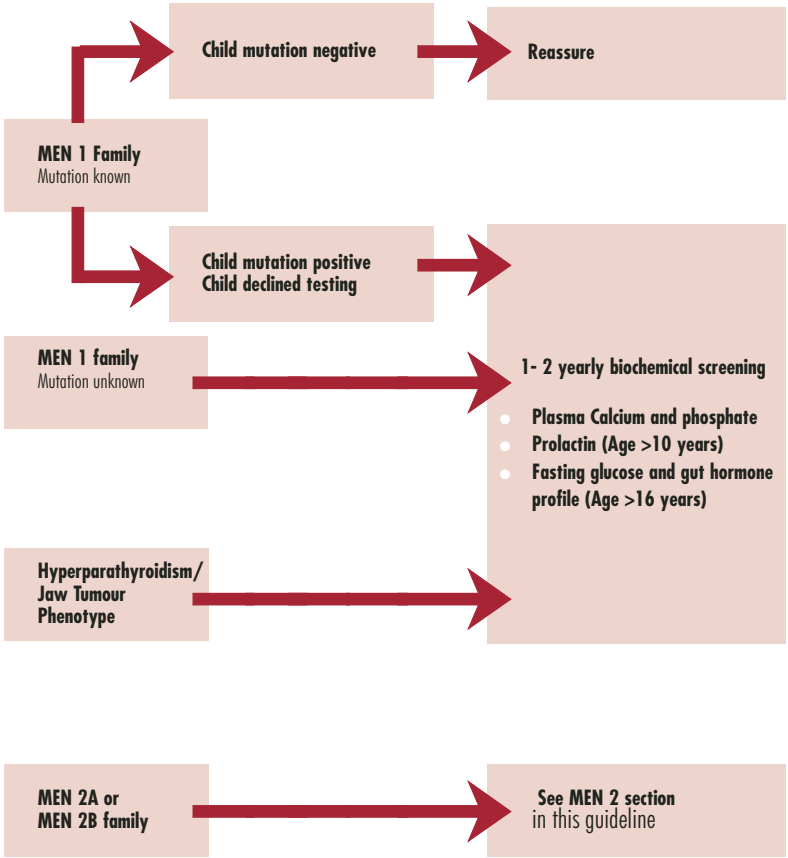
6A.7 Clinical Genetic Management of Children with a Known or Possible MEN1N Mutation *(see flow path)*

Biochemical screening for children with a MENIN mutation from known kindreds[3,20].

Serum calcium and PTH should be measured every 1-2 years from 10 years of age.

Serum prolactin measurements should be assessed from the age of 10 years, and repeated every 1-2 years. A pituitary tumour may be the first presentation in 10% of cases, prolactinoma being the most usual form, but this is very rare under the age of 10 years.*(see 6B, pituitary tumours section below).*

Pancreatic neuroendocrine tumours are uncommon in childhood. Biochemical screening is recommended from the age of 16 years with annual clinical review, fasting glucose and gut hormone profiles and measurement of chromogranin A and pancreatic polypeptide. Families should also be informed about the likely hypoglycaemic symptoms of insulinoma.



CHAPTER SIX

Chapter 6B: Pituitary Tumours in the Context of MEN 1 Syndrome

6B.1 Introduction

10% of MEN 1 patients present with pituitary tumours, usually prolactinomas (63%), [21], but this is uncommon in children. However such tumours occurring early in childhood may be the first indication of MEN 1 in a previously undiagnosed patient. Carcinomas are very rare. [22, 23]

In the absence of a family history, a pragmatic approach would be to measure PTH and serum calcium annually as part of a regular long term follow-up. A similar screen in the parents, undertaken once, is recommended.

A full discussion of the management of pituitary tumours is beyond the remit of this guideline. They are considered only as they pertain to the management of MEN 1 and need to be differentiated from other suprasellar tumours. The reader is referred to the Royal College Physicians guideline for the management of pituitary tumours and also to the craniopharyngioma section of this guideline for the differential diagnosis as well as the peri- and post-operative glucocorticoid, fluid and water balance and long term requirements of these and other suprasellar tumours.

Children with pituitary tumours have not to date been included in the UK National Registry of Childhood Tumours. It has been agreed that, with effect from the publication of these guidelines, childhood cases of pituitary tumours and family registration with the UKCCSG National Registry of Childhood Tumours are essential.

6B.2 Presentation

The symptoms of pituitary tumours may be insidious and non-specific. These include intracranial pressure symptoms and those of pituitary hypofunction and/or hormone excess.

i. Symptoms of Hypopituitarism

- Secondary Hypothyroidism (low $FT_4 \pm FT_3$ and low/normal TSH)
- Hypogonadism (delayed or arrested puberty, primary or secondary amenorrhoea)
- Hypoadrenalism (asthenia, easy fatigability, hypoglycaemia, weight loss **without** pigmentation)
- Growth hormone deficiency (short stature or growth failure)

ii. Intracranial Pressure Symptoms

- Hydrocephalus, raised intracranial pressure and visual field defects

iii. Symptoms of Hormone Excess

- Hyperprolactinaemia (causing secondary amenorrhoea, galactorrhoea)
- Cushing's disease (causing hypertension and obesity) from ACTH hypersecretion
- Gigantism more usually than acromegalic features (with possible secondary glucose intolerance) and growth hormone excess.

6B.3 Investigations

i. Biochemical

The **minimum** basal samples should include measurement of:

- prolactin with result available **before** any surgical intervention,
- FT_4 (± FT_3) and TSH to assess possibility of secondary hypothyroidism,
- LH, FSH and sex steroids in children of peripubertal age,
- 0800h and 2400h cortisol, urea and electrolytes,
- 24h urinary free cortisol,
- basal insulin-like growth factor - 1 (IGF-1) ± its binding protein (IGF-BP3),
- βHCG and AFP with result available **before** surgery to exclude a secreting suprasellar germinoma.

Other diagnostic dynamic tests in selected cases include;

- pituitary function testing in a specialist endocrine centre with appropriate facilities for sample collection, preparation, analysis and interpretation of results,
- oral glucose tolerance test (OGTT) with glucose, insulin and growth hormone measurements (to assess any secondary glucose intolerance and the inadequacy of growth hormone suppression in cases of gigantism),
- Overnight and low dose dexamethasone suppression tests in suspected Cushing's disease.

ii. Ophthalmic

Ophthalmic assessment with detailed visual fields and perimetry (± colour sensitivity) are necessary pre-operatively.

iii. Imaging

MRI is preferable to CT, providing better anatomical definition prior to surgery and more readily identifying non-tumorous pituitary lesions. This should be performed in a centre with experience. In some cases both modalities are required. In urgent cases, or in patients for whom MR is contraindicated, a CT scan is acceptable.

6B.4 Statement of Best Practice

The detailed management of children with pituitary tumours should be undertaken by a paediatric endocrinologist in a specialist tertiary and UKCCSG centre, in conjunction with a nominated pituitary neurosurgeon with paediatric experience, adult endocrine colleagues where appropriate and a clinical oncologist.

Pre- and peri-operative stabilisation and treatment of any hormone excess or deficiency syndromes are vitally important and should be undertaken in a centre with experience of these conditions.

6B.5 Management

Medical management alone may be appropriate for prolactinoma [24]

Surgical management may be required for a growth hormone secreting adenoma but medical management may be considered in selected cases.

External beam radiotherapy may be required in selected cases of failed medical and surgical treatment.

Detailed description of medical and surgical management are beyond the remit of this guideline and the reader is referred to the document; 'Pituitary tumours; recommendations for service provision and guidelines for the management of patients' published by the Royal College Physicians November 1997 ISBN 1 86016 072 7.

6B.6 Long-term Surveillance of Pituitary Tumours in the Context of MEN 1

i. Clinical

The minimum follow-up should include biochemical measures of any hormones secreted in excess, visual field perimetry and at least 6 monthly MRI assessment for between 2 and 5 years.

ii. Genetic Screening

Families with pituitary tumours secondary to MEN 1 should be referred to a centre which has adult transition and long term follow up facilities for the whole family, including biochemical and endocrine surveillance, genetic counselling, testing, and familial registration. (See above section 6A.6 +6A.7)

6.2 Information and Support for Patients and Carers with Hyperparathyroidism, Pituitary Tumours and MEN 1

Patients and their families may find the following websites and contact organisations helpful:

- AMEND: Association for Multiple Endocrine Neoplasia Disorders
  Web-site: **http://www.amend.org.uk**
- MEN Society Canada, Box 100, MEOTA, Saskatchewan, Canada SOM 1XO
  Web-site: **http://www.niddk.nih.gov/health/endo/pubs/fmen1/fmen1.htm**
- Child Growth Foundation , 2 Mayfield Avenue, Chiswick, London W4 1PW
  Telephone +44 (0)20 8995 0257 Fax +44 (0)20 8995 9075
  Email: cgflondon@aol.com; website: **http://www.childgrowthfoundation.org/**
- The Pituitary Foundation, PO Box 1944, Bristol, BS99 2UB;
  Telephone and Fax: 0845 450 0375
  E-mail: helpline@pituitary.org.uk; website: **http://www.pituitary.org.uk/disorders/**

6.3 Registration and Tumour Banking for all Patients with Pituitary Tumours, Hyperparathyroidism and MEN 1

All patients and their families should be registered with the UKCCSG tumour registry by their endocrinologist and with the regional genetics centre.

Consent to tumour banking of fresh tissue according to the UKKCCSG protocol is encouraged.

CHAPTER SIX

References

1. Thakker RV. Genetics of Endocrine and Metabolic Disorders: Parathyroid. In Reviews in Endocrine and Metabolic Disorders. Ed Kluwer Academic Publishers. 2004; 5: 37-51.
2. Pannett, A.A., Kennedy, A.M., Turner, J.J., et al. Multiple endocrine neoplasia type 1 (MEN1) germline mutations in familial isolated primary hyperparathyroidism.Clin Endocrinol 2003; 58:639-646.
3. Brandi, M.L., Gagel, R.F., Angeli, A., et al. Consensus Guidelines for Diagnosis and Therapy of MEN Type 1 and Type 2. J Clin Endocrinol Metab 2001; 86:5658-5671.
4. Rasmuson T Damber L, Johansson L, Johasson R, Larsson L-G. Increased incidence of parathyroid adenomas following X-ray treatment of benign diseases in the cervical spine in adult patients. Clin Endocrinol 2002; 57: 731-4.
5. Dijkstra B, Healy C, Kelly LM, McDermott EW, Hill AD, O'Higgins N. Parathyroid localisation–current practice. J R Coll Surg Edinb. 2002 Aug; 47(4):599-607.
6. Bilezikijian JP, Potts TJ, Ghada EF et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Clin Endocrinol Metab 2002; 87: 5353-61.
7. Burgess JR, David R, Parameswaran V, Greenaway T. The outcome of subtotal parathyroidectomy for the treatment of hyperparathyroidism in Multiple Endocrine Neoplasia Type 1. Arch Surgery 1998; 133: 126-9
8. Kramps J-L, Duh Q-Y, Demeure M, et al. Hyperparathyroidism in multiple Endocrine Neoplasia syndrome . Surgery 1992; 112: 1080-8.
9. Thakker RV. Multiple Endocrine Neoplasia. Horm Res 2001; 56(suppl 1): 67-72.
10. Carling T. Multiple Endocrine Neoplasia syndrome: genetic basis for clinical management. Current Opinion in Oncology 2005 ; 17(1): 7-12.
11. Marx SJ. Molecular Genetics of Multiple Endocrine Neoplasia Types 1 and 2. Nature Reviews Cancer 2005; 5: 367-375.
12. Carpten, J.D., Robbins, C.M., Villablanca, A., et al. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumour syndrome. Nat Genetics 2002; 32:676-680.
13. Pollock, M.R., Brown, E.M., Chou, Y.H., et al. Mutations in the human Ca (2+)- sensing receptor gene cause familial hypocalciuric hypercalcaemia and neonatal severe hyperparathyroidism. Cell 1993 ; 75:1297-1303.
14. Harris, R., Lane, B., Harris, H., et al. National Confidential Enquiry into counselling for genetic disorders by non-geneticists: general recommendations and specific standards for improving care. Br J Obs and Gynaecol 1999; 7: 663.
15. Wautot, V., Vercherat, C., Lespinasse, J., et al. Germline mutation profile of MEN 1 in multiple neoplasia type 1:search for correlation between phenotype and functional domains of the MEN 1 protein. Human Mutation 2002; 20:35-47.
16. Roijers, J.F.M., de Wit, M.J., van der Luijt, R.B., Ploos van Amstel, H.K., Hoppener, J.W.M. and Lips, C.J.M. Criteria for mutation analysis in MEN 1- suspected patients: MEN 1 case-finding. Eur J Clin Invest 2000; 30:487-492.
17. Dackew, A., Cote, G., Fleming, J., et al. Screening for MEN 1 mutations in patients with atypical endocrine neoplasia. Surgery 1999; 126:1097-103.
18. Shattuck TM, Välimäki S., Obara T., et al. Somatic and germ-line mutations of the HRPT-2 gene in sporadic parathyroid carcinoma. N Eng J Med 2003; 349: 1722-9.
19. Weinstein LS. HRPT2, a marker of parathyroid cancer.(review) N Eng J Med 2003; 349: 1691
20. Johnston, L.B., Chew, S.L., Trainer PJ, et al. Screening children at risk of developing inherited endocrine neoplasia syndromes. Clin Endocrinol 2000; 52: 127-136.
21. Trump D, Farren B, Wooding C, et al. Clinical studies of multiple endocrine neoplasia type 1. (MEN 1). Q J Med 1996; 72: 647-57.

22. Brandi, M.L. Multiple endocrine neoplasia type 1. (Review). Reviews in Endocrine &Metabolic Disorders 2000; 1:275-282.

23. Stratakis, C.A., Schussheim, D.H., Freedman, S.M., et al. Pituitary Macroadenoma in a 5-year-old: An early manifestation of Multiple Endocrine Neoplasia Type 1. J Clin Endocrinol Metab 2000; 85:4776-4780.

24. Molitch ME. Medical management of prolactin-secreting pituitary adenomas. Pituitary 2002; 5(2):55-65.